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TEHRAN LIPID AND GLUCOSE STUDY

OVER TWO DECADES OF RESEARCH TO ENSURE
OPTIMUM MANAGEMENT OF
NON-COMMUNICABLE DISORDERS

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Published online 2018 October 9. **Editorial**

Tehran Lipid and Glucose Study: A National Legacy

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Keywords: Tehran Lipid and Glucose Study, Non-Communicable Diseases, Cardiovascular Disease

The year 2018 marks 20 years since the landmark Tehran Lipid and Glucose Study (TLGS) was designed in a west-Asian developing country, the Islamic republic of Iran. With rapid economic and demographical transition in Iran in the last decades of the twentieth century (1), a dramatic risk in non-communicable diseases (NCDs), cardiovascular disease in particular, as the major cause of morbidity and mortality has occurred (2). In 1996, the National Network for Prevention and Management of Diabetes was designed and implemented as the first Iranian national project for prevention and control of NCDs (3).

In 1997, the National Supreme Council for Scientific Research called for national research projects in various scientific fields. Dr. Fereidoun Azizi, the director of Endocrine Research Center was persuaded by the late Dr. Sanei, the Vice-chancellor for Research of the Ministry of Health and Medical Education to design a proposal for survey aimed at identifying NCDs. Dr Azizi's proposal was extended to include a surveillance of a cohort for at least 20 - 30 years (4); his proposal was accepted as a national research project and his research team have described the baseline findings of TLGS in various articles, showing very high prevalence of cardio metabolic risk factors, including diabetes, hypertension and lipid profiles in the Tehranian population.

Periodic examinations and follow up of over 15000 individuals, 3 - 80 years of age, every 3 years was a great opportunity to determine the trend of various risk factors of the TLGS population in a country in nutrition transition with substantial changes in life style (5). Continuation of a cohort study, especially in a developing country is a major challenge; lack of infrastructure, influence of various factors such as culture, economy, education, and social behaviors, are the major barriers for such study. This is why many surveys are often performed to determine risk factors in populations at a particular point of time, while surveillance, systematic collection, analysis and interpretation of health data in a periodic fashion, with appropriate feedback to policymakers, is lacking in developing countries (6).

In the TLGS, following the collection of baseline data, an ongoing community-oriented life style change is being implemented. This intervention has been effective in decreasing the incidence of type 2 diabetes (7) and in diminishing the prevalence of metabolic syndrome and its components (8). Therefore, TLGS has added the aspect of "intervention" for health benefits, which has been lacking in many cohort studies, such as the Framingham heart study (9).

Inclusion of children and adolescents in the cohort of TLGS has allowed researchers to evaluate, nutrition, demographic and risk factor trends from early childhood, through adolescence into adult life. Studying these trends would be helpful to plan lifestyle and other interventions to prevent progression of risk factors to established disease in adulthood (10).

More recently, TLGS has conducted studies involving genomics and the biomarkers of NCDs and has performed the first whole-genome sequencing and launch the Iranian Reference Genome Research Project (11). Having informations on the genomes and metabolomics of this cohort with 20 years of phenotypic data could disclose many aspects of personalized medicine in endocrinology and other domains of medicine (12).

This issue of the International Journal of Endocrinology and Metabolism is dedicated to celebrating the legacy of the TLGS. We asked the researchers involved in the design, implementation, analysis, and data description and interpretation of the TLGS, to describe the key contributions of TLGS in the identification of health issues related to NCDs in the past 20 years. The authors of this special issue collectively have contributed more than 900 peer-reviewed publications related to the TLGS. We hope these

articles would be beneficial for surveys and surveillances of NCDs in the world and in particular, in developing countries.

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Published online 2018 October 22. **Review Article**

Review of Rationale, Design, and Initial Findings: Tehran Lipid and Glucose Study

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Abstract

In the late 1990s the non-communicable diseases were becoming increasingly more prevalent and a significant proportion of evidence in this regard had originated from industrialized "Western" countries. This had led to a landscape where most national and local health decisions regarding non-communicable diseases (NCDs) were informed by data generated elsewhere. Iran, as a large country in the Middle East was no exception and was going through significant population growth and urban development at the time. An initiative by the Iranian National Scientific Research Council funded an idea that was aimed at delineating the local epidemiology of NCDs and their risk factors in a manner that was unprecedented. The result was Tehran Lipid and Glucose Study (TLGS), the first and longest running cohort of its sort in Iran. Initial data out of TLGS reported the characteristics of 15005 people aged over 3 years in a representative population of Tehranians. Additionally, distribution and prevalence of cardiovascular risk factors among the study population were characterized. This population was selected through a multistage stratified cluster random sampling technique from the population of district 13 in Tehran. In addition, TLGS gave rise to a great deal of important and highly effective initial findings on national cut-off points for various variables, information about nutrition, hypertension, dyslipoproteinemia, and metabolic syndrome. TLGS also generated information about metabolic health indicators among children and adolescents. Here we present a brief overview of rationale, design, and initial findings of TLGS.

Keywords: Non-Communicable Diseases, Tehran Lipid and Glucose Study, Iran

1. Context

In the late 1990s, the spiraling epidemic of non-communicable diseases was a disturbingly palpable presence and a relatively widely accepted reality of life all over the world (World Health Report, 1998). However, the level of knowledge and evidence on these challenges varied greatly and a significant proportion of evidence in this regard had originated from industrialized "Western" countries. Therefore, decisions at national and local levels in other countries were mostly based on the evidence generated elsewhere.

Iran is a country in the Middle East region comprising a land area of 1648195 km^2 that has continuously been undergoing significant population growth and changes in its urban development over the past four decades. As one of the most advanced countries in the region in terms of science and practice of medicine and health systems, Iran has taken solid steps towards developing a sound basis for improvement of health care. For example, assessment of the epidemiological status of, and successful implementation of interventions to control, iodine deficiency disorder (1) and implementation of a national program for newborn hypothyroididsm screening (2) are two of the successful public health campaigns that have taken place over the past decades. Therefore, this country is well equipped to expand the regional knowledge of health and diseases.

Similar to other countries that have experienced rapid and significant economic and demographic alterations, Iran has experienced a period of nutrition transition (3) and the prevalence of non-communicable diseases (NCDs) has increased, making them the main health challenge and significant causes of mortality and morbidity in Iran (4-7). This trend started in the 1980s and necessitated a more active approach to epidemiological study of NCDs in Iran in a manner that could inform national policies.

2. Rationale for Design of Tehran Lipid and Glucose Study

As mentioned above, the prevalence of NCDs has been on the rise. Over the years, progress has been made in the treatment of NCD and in the pharmacological control of many risk factors. However, the most cost-effective and sustainable way of controlling these diseases is through reducing the prevalence of risk factors in a population. This can be done through lifestyle changes such as increasing regular physical activity, eating healthily and remaining tobacco-free (8-10). Along these lines, the Iranian National Scientific Research Council launched an initiative from 1995 to 1997 through which it would fund selected national research projects. The idea of Tehran Lipid and Glucose Study (TLGS) was first conceived and put forward to the Council within the above-mentioned framework in 1997. It was among the very few national projects that were funded.

Tehran city covers an area of 1500 km^2 and consists of 22 districts with a total population of over ten million people. The TLGS is a large scale community based prospective study performed on a representative sample of residents of district-13 of Tehran, capital of Iran. The TLGS was first designed in 1997 and implemented in 1999 with the aim of studying epidemiology of NCD risk factors and outcomes of NCDs in a manner that was previously unprecedented in Iran (4).

The first phase of TLGS was a cross-sectional study on residents of district 13 in Tehran (between 3 to 69 years of age) that assessed the prevalence of cardiovascular diseases and their risk factors (Figure 1). The second phase, however, started in 2002 and was designed as a longitudinal study with an anticipated duration of at least 20 years, which has continued to date. Data collection in this phase was planned to be performed in 3-year intervals. A detailed explanation of the study population, baseline measurement and follow-up visits have been presented before (3). The year 2018, marks the start of the seventh 3-year data collection cycle.

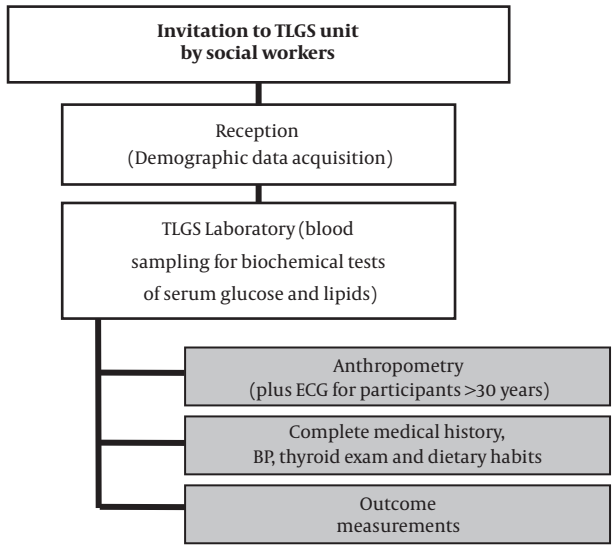

Figure 1. Study design of the phase I of the TLGS. Abbreviations: TLGS, Tehran Lipid and Glucose Study; ECG, Electrocardiogram; BP, Blood Pressure.

3. Initial Findings of Tehran Lipid and Glucose Study

3.1. Initial Characteristics of the Study Population and Demographic Findings

Initial data out of TLGS reported the characteristics of 15005 people aged over 3 years in a representative population of Tehranians. Additionally, distribution and prevalence of cardiovascular risk factors among the study population were characterized. This population was selected through a multistage stratified cluster random sampling technique from the population of district 13 in Tehran. At the time, Tehran was composed of 20 urban districts and made up a population of 6.7 million (Iran National Census 1996). District 13 was chosen mainly because city-wide data showed a high rate of stability in that district. Also, the age distribution in district 13 was representative of the overall population in Tehran.

The study population comprised 15005 Tehranian children, adolescents, and adults, 44% males and 56% females. Nearly, 5% of the study population was between 3 - 6 years, 6% between 7 - 10 years, 9% between 11 - 14 years, 19% between 15 - 24 years, 17% between 25 - 34 years, 16% between 35 - 44 years, 12% between 45 - 54 years, and 10% between 55 - 64 years, and 7% over 64 years. Age and sex distributions are shown in Table 1.

Initial findings of TLGS shed some much anticipated light on the smoking habits of the Tehranian population older than 15 years of age. It was shown that 10.6% of the population were daily smokers, while 1.5% were occasional smokers, 6.1% ex-smokers, and 81.8% non-smokers.

Moreover, other key demographic information became available within the context of TLGS (some of the more important ones are summarized in Table 2).

3.2. National Cutoff Points

A major contribution of TLGS that became tangible in its early years was defining cutoff points that were spe-

Table 1. Age Distribution of Tehran Lipid and Glucose Study (TLGS) Participants Based on the WHO STEPS Categories[a]

Age Groups (y)	Men	Women	Total
3 - 6	336 (49.1)	349 (50.9)	685 (4.6)
7 - 10	469 (49.2)	484 (50.8)	953 (6.4)
11 - 14	667 (49.9)	670 (50.1)	1337 (8.9)
15 - 24	1195 (42.0)	1650 (58.0)	2845 (19.0)
25 - 34	985 (39.8)	1489 (60.2)	2474 (16.5)
35 - 44	1011 (42.6)	1360 (57.4)	2371 (15.8)
45 - 54	724 (39.8)	1094 (60.2)	1818 (12.1)
55 - 64	624 (43.0)	827 (57.0)	1451 (9.7)
≥ 65	599 (55.9)	472 (44.1)	1071 (7.1)
Total	6610 (44.1)	8395 (55.9)	15005 (100.0)

[a]Values are expressed as number (%).

Table 2. Important Demographic Characteristics of Tehran Lipid and Glucose Study (TLGS) Participants at Baseline

	No. (%)
Marital status (age ≥ 15)	
Single	3071 (25.5)
Married	8328 (69.2)
Divorced/widowed	631 (5.3)
Literate[a] (age ≥ 7)	
Men	5997 (95.6)
Women	7246 (90.1)
At least one university degree (age ≥ 20)	
Men	746 (18)
Women	515 (10)
Employed (age ≥ 10)	
Men	3195 (62)
Women	606 (9)

[a]Literate is defined as being able to read and write.

cific to an Iranian population for various variables. One of the early reports from TLGS reported cutoff points for anthropometric measures as indicators of cardiovascular risk factors in an Iranian population of 10522 (11). Results of this study suggested that many of these cutoff points were higher for the Iranian population compared with other Asian populations. Studies with such intentions continued in the TLGS and population-specific cutoff values for many other parameters were defined. Some of these values, for example that for TSH, are reviewed in various articles in this issue.

3.3. Nutrition

TLGS was designed and has been conducted and maintained with the importance of nutrition and nutritional interventions in mind. This perspective came to fruition not very long after the start of this cohort. Initial assessment of nutritional habits of the TLGS population resulted in a comparison between mean servings of intakes of various food groups among Tehranians and those set forth in the Food Guide Pyramid (Figure 2) (12). A cross-sectional study on 403 TLGS participants older than 25 years of age was designed and conducted to assess diet and energy expenditure and requirement of adults in Tehran. The findings revealed that an average Tehranian has an energy requirement that is lower than daily allowances recommended by FAO/WHO and highlighted the need for interventions aimed at improvement of dietary habits in urban populations in Iran (13). Another seminal study by Esmaillzadeh et al assessed the relationship between whole-grain intake and metabolic syndrome from an epidemiological perspective. This study showed that diets rich in whole-grain are inversely correlated with the risk of metabolic syndrome (14) and it was one of the few studies that had addressed such a diet-disease relationship in a large population at the time. Many later studies in TLGS addressed nutritional findings and are thoroughly reviewed in a review article in this issue.

3.4. Blood Pressure and Hypertension (15)

As TLGS was designed to assess the status of cardiovascular risk factors and to subsequently inform national policies on approaching these risk factors (4), it was well equipped to produce information on hypertension as a major modifiable cardiovascular risk factor. Epidemiological data on the status of hypertension in Iran was available when the TLGS was started, however, the sample size and sampling method of the TLGS gave it a unique position in this regard. Initial findings in the TLGS showed that mean systolic and diastolic blood pressure were higher in men than in women (119.5 ± 17.1 vs. 116.1 ± 16.8 mmHg, $P < 0.001$ for systolic and 77.4 ± 10.8 vs. 76.9 ± 10.0 mmHg, $P < 0.05$ for diastolic blood pressure). A crude prevalence rate of 22.9%, with an age-adjusted prevalence of 20.4% (CI 95%: 19.2 - 21.6) for men and 25.1% (CI 95%: 24.0 - 26.2%) in women ($P < 0.001$), was reported (4). These prevalence data was not totally similar to previous reports, which could be due to differences in sample size, environmental and cultural factors.

More analyses of the initial TLGS data demonstrated an increase in the prevalence of hypertension with age in both sexes. Hypertension in 20 - 29 year-old men was about twice that of women of the same age group. While no difference was detected between men and women in the 30 - 39 year-old group, in adults 40 years and over hyperten-

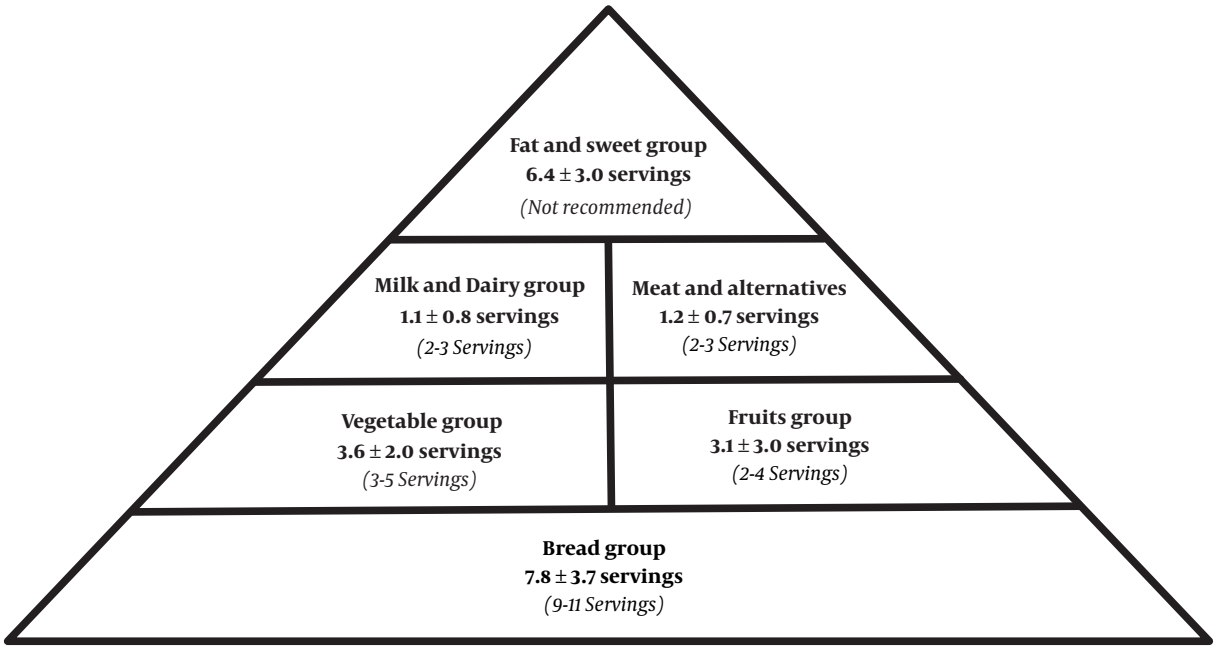

Figure 2. Mean servings of intake of various food groups in the TLGS population in comparison with the Food Guide Pyramid. Values in **Bold** are from TLGS, and Food Guide Pyramid values are presented in *Italics*.

sion was more prevalent in women than in men. The reported age and sex-specific differences in hypertension in TLGS were generally consistent with other studies despite subtle differences. Studies on hypertension in TLGS has been ongoing and a review of all the findings is presented in a separate article in this issue.

In its initial years, the TLGS was used as a powerful tool to address more profound questions that were subjects of extensive controversies. In one instance, TLGS researchers questioned the relative significance of systolic and diastolic blood pressure (SBP and DBP) measurements in classification of hypertension according to the international standard of Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-IV) (16). This study concluded that the role of SBP in classification of hypertension according to JNC-VI was more significant only in older adults, and that DBP had a more prominent role in other age groups.

TLGS helped the investigator ask more directed questions regarding NCDs. For instance, another aspect of blood pressure that was assessed within the context of TLGS was the status of blood pressure in adult population in Tehran with myocardial infarction (MI). Since all TLGS participants undergo an electrocardiography (ECG), a group of participants were selected and their ECG tracings were analyzed according to Minnesota ECG coding criteria and categorized as "probable/possible MI" or "no MI". The mean of two separate blood pressure measurements for each participant was also measured and the prevalence of MI in relation to an index of hypertension was assessed (17). This study revealed that among the population in Tehran, MI was more prevalent in hypertensive patients and that after adjustment for age, sex, and body mass index, patients with ECG-defined MI had significantly lower diastolic blood pressure. This study also provided some information about pulse pressure and how it related to blood pressure in the presence or absence of MI. Many similar studies have since tried to elaborate on the causes and associated risk factors of NCDs within the context of TLGS.

3.5. Dyslipoproteinemia

A less thoroughly investigated area in Iran at the time when TLGS was initiated was the prevalence of dyslipoproteinemia and distribution of lipoprotein values in urban regions. This coincided with assimilation of more Western lifestyle habits in terms of diet and physical activity by the Iranian population. An epidemiological survey conducted within the framework of TLGS (18) aimed to address this issue and revealed that Tehranian adults had higher levels of total cholesterol, LDL cholesterol (LDL-C) and triglycerides,

and slightly lower HDL cholesterol (HDL-C) compared with data reported by similar studies in other industrialized countries.

In another early report (19), TLGS investigators performed a more thorough assessment of HDL-C as a common lipid disorder in coronary artery diseases in the TLGS population and highlighted age, sex, hypertriglyceridemia, obesity, truncal obesity, cigarette smoking and passive smoking as determinants of HDL-C. Further studies in later years continued to elaborate on the status of dyslipidemia in the context of TLGS and an overview of the findings of these studies are presented in an article in this issue.

3.6. Diabetes Mellitus, Impaired Glucose Tolerance and Metabolic Syndrome

Among the most important initial findings of TLGS was the prevalence of known diabetes mellitus, new cases of diabetes mellitus (DM), and impaired glucose tolerance (IGT) among different age groups in an adult population in Tehran (Figure 3). These findings highlighted the fact that in both sexes, there was an increase in the prevalence of both DM and IGT (4).

At around the time of TLGS initiation, a number of studies in Iran had reported the prevalence of individual cardiovascular risk factors. However, an analysis of these risk factors as a cluster was not available. TLGS presented an opportunity for examining the prevalence of such a cluster that is known as metabolic syndrome. In one of the early publications out of TLGS, Azizi et al. performed a thorough analysis of various components of metabolic syndrome based on ATP III (adults treatment panel III) criteria and found the age-standardized prevalence of metabolic syndrome in Tehran to be 33.7% (CI 95%: 32.8 - 34.6), which was higher than what many studies had reported at the time (20). They also showed that this syndrome was more common among women, with the most common metabolic abnormality being low HDL cholesterol. The pattern, trend and other aspects of this syndrome were further analyzed in more details in future studies. Moreover, TLGS reported cumulative incidence of cardiovascular (CV) risk factors in different age groups in adults (Figure 4).

3.7. Findings on Children and Adolescents

When TLGS was launched, a few scattered studies had evaluated lipid profiles in the Iranian population in general, and more specifically in the pediatric and adolescent population in Iran (21, 22). This type of information was not readily available even in the Middle East as a region. Less than three years from its conception, TLGS provided a detailed report on the status of serum lipid levels in a representative population of Iranian children and adolescents in an encompassing article (23), highlighting specifications of dyslipoproteinemia in the Iranian children and adolescents in comparison to global reports. Most importantly, this report showed that this population suffered higher TC, TG, and LDL-C levels and lower HDL-C levels; and that the age distribution of dyslipoproteinemia was different. As such, it set the stage for further national epidemiological research in this field, while providing evidence for designing more precise and efficient health policies and public health campaigns in an era of lifestyle shift in Iran.

This was not the only early TLGS study that looked at a burdensome health issue in adolescents. In an initial report out of TLGS, hypertension among children and adolescents was reported to be slightly more prevalent in boys than in girls, although the difference did not reach statistical significance in that analysis (12.7% vs 10.9%, NS) (4). One comprehensive study set out to determine predictors of cardiovascular disease (CVD) risk factors in the adolescent population of TLGS through the use of anthropometric measurements, dietary recall interviews, blood pressure measurements and lipid profiles. The results revealed strong positive correlations between BMI and blood pressure (both systolic and diastolic) in boys and girls. Some other dietary and lifestyle factors were also identified as predictors of CVD risk factors (24). Moreover, TLGS delineated the cumulative frequency of CVD risk factors in different age groups of Tehranian children and adolescents (Figure 5) (4). Future studies in TLGS also focused on children and adolescents and to date, this population has been an important component in TLGS.

4. Discussion

Initial findings from TLGS highlighted that the prevalence of CV risk factors were considerably high among the adults in a population that, at the time, was representative of the Iranian population. The reported figures were higher than those in industrialized countries such as Canada and the United States (25-28). This included a lower prevalence of antiatherogenic factors such as HDL-C compared with industrialized countries (25). Low HDL-C could be associated with high saturated fat intake and low physical activity (29, 30), both indicators of unhealthy lifestyles. Despite these alarming findings, CVD mortality rates were lower in Iran compared to industrialized countries, probably due to the lower prevalence of hypertension in Iran

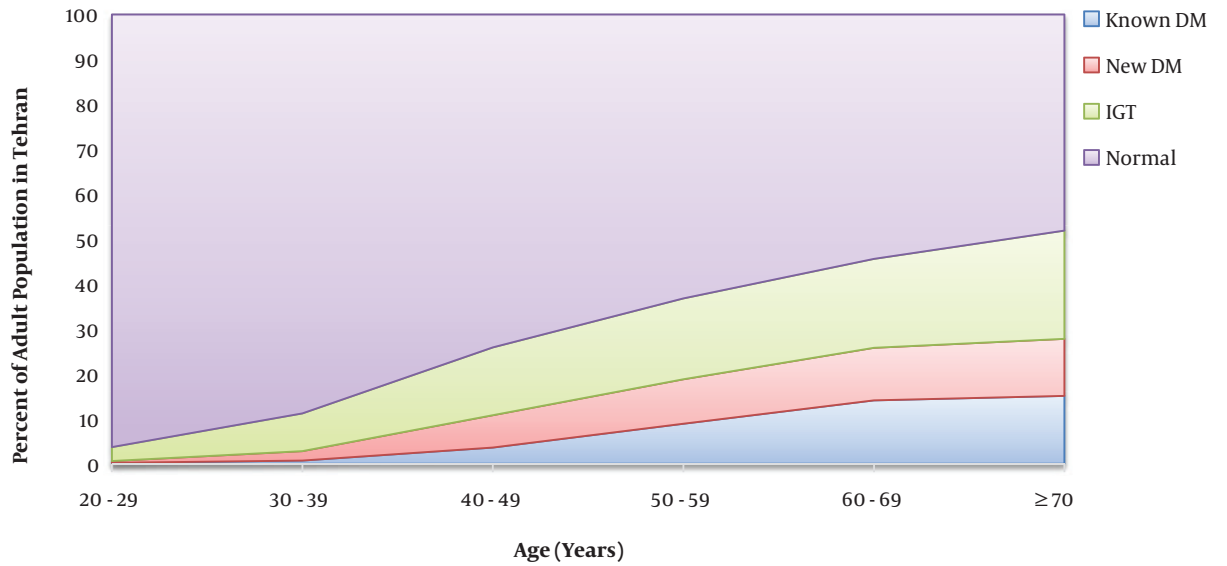

Figure 3. Prevalence of diabetes (DM) and impaired glucose tolerance (IGT) in Tehranian adult population; Tehran Lipid and Glucose Study, Adapted from reference (4).

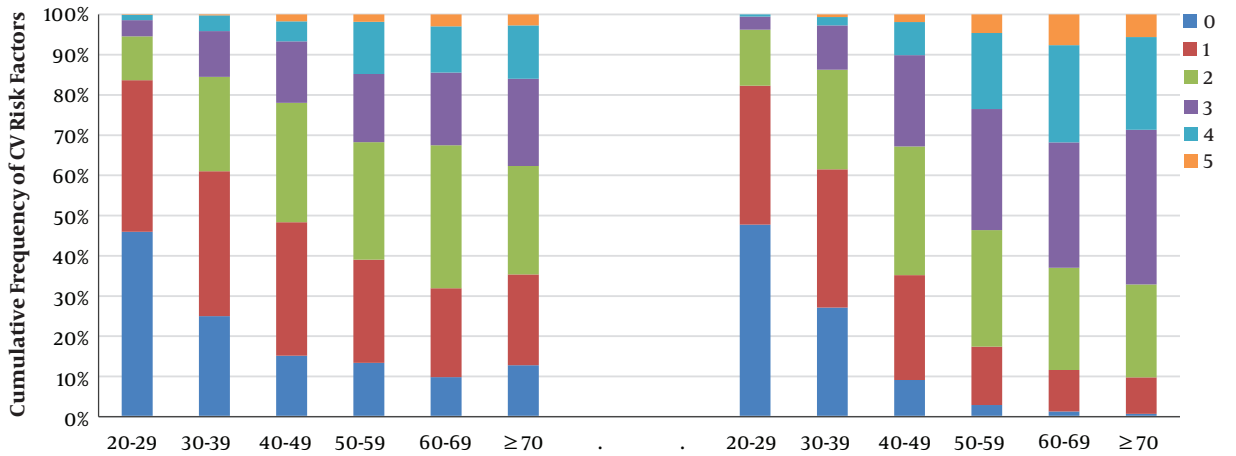

Figure 4. Cumulative frequency of cardiovascular risk factors in adults including hypertension, generalized obesity, central obesity, smoking, diabetes mellitus, total cholesterol ≥ 240 mg/dL, LDL cholesterol ≥ 160 mg/dL, HDL cholesterol < 35 mg/dL, and triglycerides ≥ 400mg/dL in Tehranian adult population, Tehran Lipid and Glucose Study, Adapted from reference (4).

(26-28). More worrying was the fact that children and adolescents followed a similar pattern and the percentage of Iranian children and adolescents with one or more CV risk factors was higher than the reports out of the United States (31-33). This indicated that a higher mortality among the adult population and a future adult life with significant metabolic and CV morbidity for the children and adolescents were expected in Iran.

The figures reported in the initial phases of the TLGS also differed with those out of other countries in the region. For instance, mean LDL-C concentrations, a major atherogenic lipoprotein, in women in Tehran was higher than those reported in Saudi Arabia (34). Such differences in observations suggested that variations in metabolic health parameters existed in the same geographical region and that many factors were at play and needed to be identified.

In conclusion, this paper highlights the findings of the initial stages of TLGS and points to the alarming trends in the cardiovascular risk factor and nutritional changes

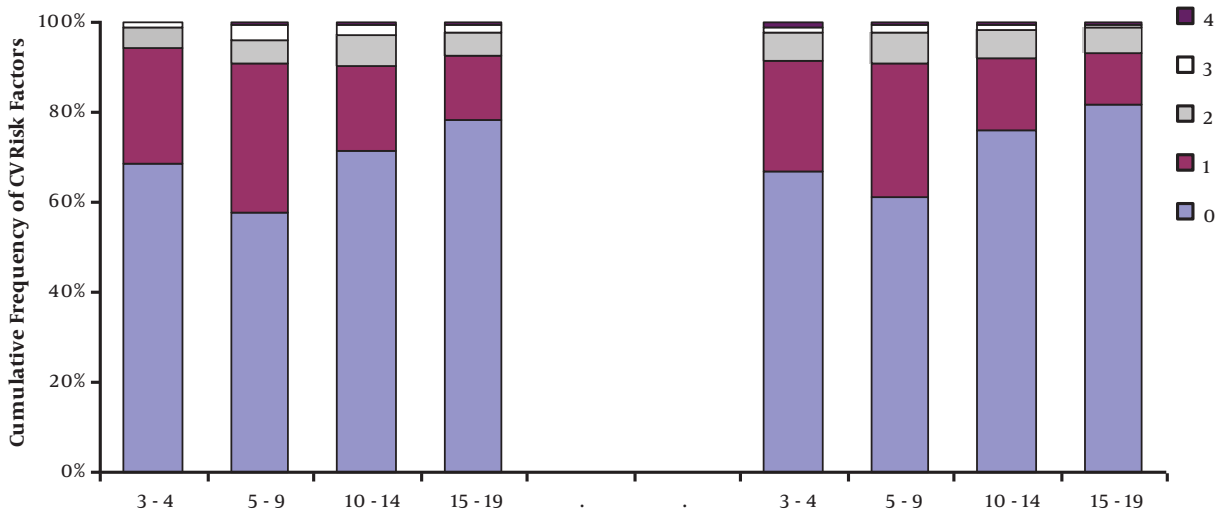

Figure 5. Cumulative frequency of cardiovascular risk factors in children and adolescents including hypertension, obesity, total cholesterol ≥ 95th, LDL cholesterol ≥ 95th, HDL cholesterol < 5th, and triglycerides ≥ 95th percentile for each age group of children and adolescents, Tehran Lipid and Glucose Study, Adapted from reference (4)

in Iran at that time. The findings revealed the transition in nutrition and lifestyle that Iran was, and still is, going through. By showing that more than half of adults at the time were at increased risk of cardiovascular and metabolic diseases, and that children and adolescents in Iran were *en route* to a more morbid adulthood, TLGS became of significant assistance in designing and implementation of prevention programs, public health policies, health education programs, and an integrated public health approach. This landmark initial study became the stepping stone for an interventional phase of TLGS which resulted in crucial and valuable findings in the future.

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Published online 2018 November 4. **Review Article**

Nutrition and Diabetes, Cardiovascular and Chronic Kidney Diseases: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: The high prevalence of chronic diseases can be prevented or managed by specific changes in lifestyle patterns of individuals of which dietary factors is emphasized. The objective of this study was to review all findings of the Tehran Lipid and Glucose Study regarding validity and reliability of food frequency questionnaire (FFQ), evaluating dietary quality and association of dietary factors in relation to diabetes, dysglycemia, cardiovascular (CVD) and chronic kidney disease (CKD).
Evidence Acquisition: Related documents were searched through PubMed and Scopus databases, in English language from 2000 to 2017. Finally, 52 relevant documents were eligible for inclusion in this review.
Results: The FFQ proved to be an acceptable tool for assessing nutrient and food group intakes and rank individuals accurately according to the levels of their dietary intakes. After 8 years of follow-up, the western dietary pattern (DP) was fairly stable but there was instability of traditional Iranian DP. DPs of over two-thirds of Tehranian populations were not in accordance with the dietary recommendations. Higher dietary scores of variety and healthy DPs were also associated with reduced odds of dysglycemia. The main dietary factor related to increased risk of CVD in our population was western DP. Patterns of amino acid intakes may contribute to the development of CVD. Higher intakes of several micronutrients and macronutrients, DPs and some vegetables decrease the risk of CKD. In conclusion DPs of most Tehranian adults need improvement.
Conclusions: This review showed that higher adherence to healthy food choices was associated with reduced odds of dysglycemia and CVD. Dietary sources of renal-protective nutrients should be encouraged among the general population.

Keywords: Chronic Kidney Disease, Diabetes, Cardiovascular Disease, Diet, Nutrients, Tehran Lipid and Glucose Study

1. Context

The high prevalence of chronic diseases such as type 2 diabetes (T2DM), cardiovascular (CVD) and chronic kidney disease (CKD) is becoming a major public health concern in most countries, although this can be avoided or managed by specific changes in lifestyle patterns of individuals (1). One such change is dietary factors; hence the accurate estimation of dietary intakes is crucial (2). To prevent inaccurate estimations of dietary intakes leading to incorrect data on the association between diet and disease, the reproducibility and validity of measurement tools is vital (3).

The importance of healthful dietary pattern (DP) has been emphasized using dietary guidelines and recommendations. The diet quality has been evaluated, by assessing adherence to dietary guidelines to identify inappropriate DPs, and implementing timely policy revisions and strategies (4, 5).

Dietary factors related to chronic disease may differ across populations because of cultural, social and genetic differences. In this regard limited and inconsistent data are available from developing countries (1). Recently the role of different DPs such as the Mediterranean diet (MD) (6) or dietary approach to stop hypertension (DASH) (7, 8), functional foods (9), nutraceuticals (10) and patterns of amino-acid intakes (11) has been emphasized in the prevention and management of cardio-metabolic diseases. On the other hand, in recent decades consumption of unhealthy foods like sugar sweetened beverages, fast foods,

salty and sweet snacks, hydrogenated and animal fats has shown a fast increasing trend worldwide, which is associated with high incidence of chronic diseases (12, 13). The Tehran Lipid and Glucose Study (TLGS) is an ongoing study started in 1999 with a representative sample of 15005 individuals, aged $\geq$ 3 years, recruited from among residents of district no.13 of Tehran, the capital of Iran (14). This prospective study provides an opportunity to study different aspects of NCDs in this Middle-Eastern population.

The objective of this study was to review all findings of studies conducted within the framework of TLGS regarding the validity and reliability of the food frequency questionnaire (FFQ), used for evaluating dietary quality and association of dietary factors in relation to T2DM, dysglycemia, CVD and CKD to provide a deeper insight into these diseases in this population in order to design better preventive strategies for high risk individuals at high risk for these diseases.

2. Evidence Acquisition

In this review, related documents were searched in England language through PubMed, Scopus, and Embase databases, 2000 to 2017. To obtain studies focusing on reliability and validity of TLGS food frequency questionnaire, overall diet quality and nutritional behaviors of TLGS population, we used different combinations of "diet", "nutrition", "food frequency questionnaire", "quality", habit", "validity", and "reliability". Following key words were used to search papers investigating potential relations between dietary factors and risk of cardio-renal diseases and diabetes: "diet", "nutrition", "cardiovascular", "kidney disease" and "type 2 diabetes". Finally, 52 relevant documents were eligible for inclusion in this review. Three papers focused on development of the TLGS, the FFQ, and its validity and reliability. Dietary habits and diet quality of TLGS population were described in 9 papers. The associations of dietary factors with the prevalence or incidence of CVD events, CKD, T2DM or dysglycemia were investigated in 6, 9 and 28 papers, respectively.

3. Results

3.1. Reliability and Validity of Food Frequency Questionnaire

The FFQ, one of the most commonly simple and practical methods used to evaluate usual long-term dietary intakes in epidemiological studies, was developed for the TLGS. The FFQ is consists of food items standard serving size commonly consumed by 132 Iranians subjects. The reliability and validity of this FFQ was evaluated using twelve 24-hour dietary recalls repeated every month, two FFQs (completed one year apart) and comparing dietary intakes with serum and urine biomarkers. The results showed relative validity and good reliability of the FFQ for nutrient intakes and main food groups and accurate ranking of individuals, based on nutrient and food group intakes (2, 3). Mean adjusted and deattenuated correlation coefficients between the 24-hour-DR and FFQ2 were 0.53 and 0.39 in men and women, respectively. Mean adjusted intraclass correlation coefficients between the two FFQ's were 0.59 and 0.60 in men and women, respectively (3). For food groups, median correlation coefficients between the 24-hour-DR and FFQ2 were 0.44 and 0.37 in men and women, respectively. The median of adjusted intra-class correlation coefficients were 0.52 and 0.57 in men and women, respectively. This FFQ can be an acceptable tool for assessing nutrient and food group intakes in this population and rank individuals accurately according to the levels of dietary intakes.

Moreover obtaining DPs yields a better perception of dietary habits and various combinations of foods consumed. Hence, the reliability and comparative validity of DPs using FFQ data shows precision and accuracy of extracted patterns; the stability shows the constancy of DPs when it may have changed. There was strong reliability between two FFQs and reasonable validity for the two extracted DPs; Iranian traditional and western DPs. After 8 years of follow-up, the western DP remained fairly stable whereas there was instability of Iranian traditional DP over the follow-up years (15). Hence this FFQ is an acceptable tool for determining DPs of Iranians to investigate the relationship of DPs with health outcomes in epidemiological studies.

3.2. Dietary Quality

Consumption of a wide number of foods and food groups (variety) was included as part of dietary recommendations. Mean dietary diversity score (DDS) was 6.25 $\pm$ 1.08 (ranged 0 -10) in adolescents and had a positive correlation with mean adequacy ratio of nutrients (16). Mean DDS were 6.05 $\pm$ 1.02 and 6.01 $\pm$ 1.0 in men and women, respectively, both were associated with the nutrient adequacy (5, 17).

The mean healthy eating index (HEI) score was 64.9 $\pm$ 9.6 in boys and 64.8 $\pm$ 9.4 in girls (range 0 - 90); diets of most Tehranian adolescents (74%) needs improvement (18).

The mean $\pm$ SD score for dietary guidelines for American adherence index (DGAI) 2005 was 8.31 $\pm$ 1.9 (range 2.5 - 15.0); about two-thirds of participants achieved less than

half of the possible scores of the DGAI (19). Compliance of the WHO/FAO nutrition targets for n-3 poly-unsaturated fatty acids (PUFAs), sodium, fruit and vegetable intakes was weak and the largest disparity with recommendation was seen for n-3 PUFAs (4).

The above findings reveal that DPs of over two-thirds of Tehranian population were not in accordance with dietary recommendations, indicating that unbalanced dietary intakes of Tehranian population must be examined for timely policy revisions, and implementation of dietary interventions strategies to promote diet quality.

3.3. Dietary Behaviors

Age, educational level, gender and marital status were items that impact the nutritional knowledge, attitude and practice of Tehranian adults (20). Moreover dietary behavior of adolescents may not be based on their nutritional knowledge of adolescents; 82% of girls and 75% of boys had good nutritional knowledge, while 25% of boys and 15% of girls had good nutritional practice (21).

3.4. Under-Reporting of Energy Intakes

Obese subjects had the highest rate of under-reporting of energy intake. The amounts of macro- and micronutrient intakes were lower in under-reporters compared to normal-reporters (22).

3.5. Nutrition, Diabetes and Dysglycemia

In a nested case-control study conducted on 178 patients with T2DM and 520 matched controls, associations between total dairy intakes, different dairy subtypes and major DPs with odds of T2DM were investigated. Odds of T2DM decreased 27% for each 100 g/day increase in total dairy intake (95% CI = 0.52 - 1.02; P = 0.064). The odds of T2DM was also significantly lower in individuals with highest intake of milk (tertile 3) compared to lowest (OR = 0.62, 95% CI = 0.38 - 0.99) (23). A higher score of traditional DP, characterized by high intakes of whole grains, legumes, eggs, and red meat was associated with reduced odds of T2DM (OR per 1-SD = 0.82, 95% CI = 0.67 - 0.99) (7). A prospective study of 904 adults followed for 3 years showed that the odds of IGT was significantly higher in those with highest adherence to the western DP, compared to lowest (OR = 3.09, 95% CI = 1.28 - 7.50) (24). No significant association was observed between the Dietary inflammatory index (DII) and odds of glucose intolerance or T2DM in a cross-sectional study of 2975 adults (9).

The odds of T2DM after 6-years of follow-up was significantly lower in those with weekly nut intakes of 2 - 3.99 serving (quartile 3; OR = 0.51, 95% CI = 0.26 - 0.97)) and intakes of $\geq$ 4 serving (quartile 4; OR = 0.47, 95% CI = 0.25 - 0.90), compared to those with an intake of < 1 serving per week (quartile 1) (25). No significant association was observed between usual intake of allium vegetables (garlic and onion) and incidence of T2DM after 6 years of follow-up (1). The risk of T2DM increases with higher intakes of total nitrite (HR = 2.43, 95% CI = 1.45 - 4.05) and animal-based (HR = 1.88, 95% CI = 1.12 - 3.15) only in individuals with a low intake of vitamin C. No significant association was observed for nitrate (26).

Food security did not differ significantly between diabetic (2.38 ± 2.1) and non-diabetic (2.25 ± 2.5) adults (6).

The odds of T2DM was significant lower in quartile 4 compared with quartile 1 of whole grains (OR = 0.88, 95% CI = 0.80 - 0.94); the odds of having FBG $\geq$ 110 mg/dL as a component of MetS was gradually decreased by increasing the quartiles of whole grain intakes (Ptrend = 0.04) and becoming significant in those with the highest intake compared to those with the lowest intake (OR = 0.75, 95% CI = 0.63 - 0.90) (27). In a case-control study, an inverse association was reported between legumes intake and FBG (28).

In a cross-sectional study of 581 healthy adults, mean FBG was significantly lower in those with the highest DDS quartile than in the lowest (86 ± 5 vs. 91 ± 5 mg/dL; P < 0.05). The odds of having FBG $\geq$ 110 mg/dL decreased significantly across quartiles of the DDS (Ptrend = 0.02) (29). Mean FPG and odds of having FPG $\geq$ 100 mg/dL significantly reduced across quartiles of the DGAI-2005 score (19). The effects of a weight reducing diet and DASH diet on metabolic components were compared on 116 adults with MetS in a randomized clinical trial. After 6 months adherence to the DASH diet, FPG decreased significantly in both men and women (30).

In two cross-sectional studies of adults, dietary fatty acid composition including intakes of SFA, oleic acids, linoleic acids (31), and PUFA either $\omega 3$ or $\omega 6$, and the $\omega 6/\omega 3$ ratio showed no significant associations with FPG and odds of having FPG $\geq$ 100 mg/dL (32). However, one cross-sectional study of 2750 adults, reported an inverse associations for FBG with total PUFA intake (β = -0.27) and with ratio of PUFA-to-SFA ratio (β = -0.05) (20). In a cross-sectional study of 2537 adults, FBG was positively associated with total protein intake (β = 0.06 in men and β = 0.11 in women, P < 0.05) and negatively associated with animal-to-plant protein ratio (β = -0.078 in men and β = -0.056 in women, P < 0.05) (33). Dietary total anti-oxidant capacity (TAC) was negatively associated with FBG after a 3-year follow-up of 1983 adults but odds of having FBG $\geq$ 100 mg/dL did

not differ significantly across quartiles of TAC intakes (34). The odds of having FBG $\geq$ 110 mg/dL was significantly decreased across quartiles of flavonoid intakes (P < 0.005) and increased across quartiles of lignan intakes (Ptrend = 0.039) (35). An inverse significant association was observed between magnesium intakes and FBG concentrations (β = -0.08, 95% CI = -0.76, -0.017) (36). FBG or odds of FBG $\geq$ 100 mg/dL was not significantly associated with fructose intake (37), phytochemical index (38), glycemic index and glycemic load (39), or HEI-2005 (40). Higher adherence of LCD was not associated with higher odds of elevated blood glucose levels after 3.6 years follow-up in children and adolescents, aged 6-19 (41). After 3.6 years of community lifestyle modification aiming at improving nutrition intakes, physical activity, and smoking cessation, the number of participants with high FBG in the intervention group was significantly lower than that observed in the control group (23.7% vs. 29%, P < 0.001) (42).

A 3-year follow-up of participants in the TLGS showed that higher intake of green fruits and vegetables was negatively related to change of FPG (β = -0.02, P = 0.04) in women whereas in men higher intake of red/purple fruits and vegetables was related to FPG (β = -0.08, P = 0.05) (43). In a cross-sectional analysis of 4677 adults aged (19 to 84 years) an increased chance of having abnormal glucose homeostasis was observed in subjects who had higher intakes of SFAs along with high-fat diet (OR = 1.32, 95% CI = 1.06 - 1.65) (44). The risk of high FBG (OR = 2.43, 95% CI = 1.23 - 4.81) and IFG/IGT (OR = 2.94, 95% CI = 1.55 - 5.57) also increased per 1 SD increase of the visceral adiposity index DP, characterized by high intake of fried vegetables, vegetable oils (except olive oil), salty snacks, legumes, eggs, fast foods and low intake of traditional sweets, high and low fat dairy, cruciferous vegetables, sugars and honey (45). In a 3-year follow-up of healthy children and adolescents, higher adherence to DASH diet led to decreased incidence of high FBG (OR = 0.40, 95% CI = 0.15 - 0.99, highest compared to the lowest quartile, Ptrend = 0.038) (46). In another prospective analysis, FBG was inversely related to LCD score (β = -0.002, 95% CI = -0.005, -0.001) (47).

Overall, based on findings of TLGS, higher intakes of legumes, total PUFA, PUFA-SFA-ratio, animal-to-plant protein ratio, TAC, and magnesium were associated with lower FPG while FPG significantly increased by higher intakes of total protein. The risk of high FPG was decreased by higher intakes of whole grain and flavonoids while higher intake of lignin increased odds of having high FPG. Higher dietary scores of DDS, DGAI, and DASH were also associated with reduced odds of high FPG.

Higher adherence to the traditional Iranian diet, and higher intakes of total dairy, milk, and nut were associated with reduced odds of T2DM, although the risk of T2DM increased with higher intake of dietary nitrite in those with low vitamin C intake (Figure 1).

3.6. Nutrition and Cardiovascular Disease (CVD)

Several dietary factors were identified as potential risk factors of cardiovascular events in our population; Western DP score (HR = 2.07, 95% CI = 1.03 - 4.18) and a high-fructose diet (HR = 1.81, 95% CI = 1.04 - 3.15) was accompanied with an increased risk of CVD (12, 48), whereas higher intake of allium vegetables was related to 64% reduced risk of CVD outcomes (HR = 0.36, 95% CI = 0.18 - 0.71) (1). Our novel data also revealed that amino acid patterns of diet may also contribute to incidence of CVD (49); the amino acid pattern with a higher load of glycine, cysteine, arginine and tryptophan, was negatively related to CVD (HR = 0.28, 95% CI = 0.09 - 0.88); higher consumpton of sulfur-containing amino acids (cysteine and methionine), and potentially cardio-protective amino acids (arginine, cysteine, glutamic acid, glycine, histidine, leucine and tyrosine) had a 73% (HR = 0.27, 95% CI = 0.09 - 0.86) and 74% (HR = 0.26, 95% CI = 0.09 - 0.78) decreased risk of CVD events; however higher intakes of glutamic acid and proline increased the risk of CVD (49). We also showed that higher intake of plant derived L-arginine may have a protective effect whereas animal-derived L-arginine may be a risk factor for development of hypertension and CHD events (Figure 2) (50).

Main dietary factor related to increased risk of CVD in our population was western DP, whereas higher consumption of allium vegetables had a protective effect. Our novel analysis also revealed that pattern of amino acid intakes may contribute in the development of CVD.

3.7. Nutrition and Chronic Kidney Disease

Previous studies in the framework of the TLGS, conducted on the association of dietary factors with kidney function, estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease study equation and CKD was defined as eGFR < 60 mL/min/1.73 m^2.

In a cross-sectional study of adults without T2DM, the ORs (95% CI) of CKD in the highest quartile compared to lowest quartile, were 0.70 (0.51 - 0.97) for plant protein, 0.73 (0.55 - 0.99) for PUFA, and 0.75 (0.57 - 0.97) for ω6 fatty acids, although the ORs (95% CI) of CKD in the highest quartile of animal protein, compared to the lowest was 1.37 (1.05

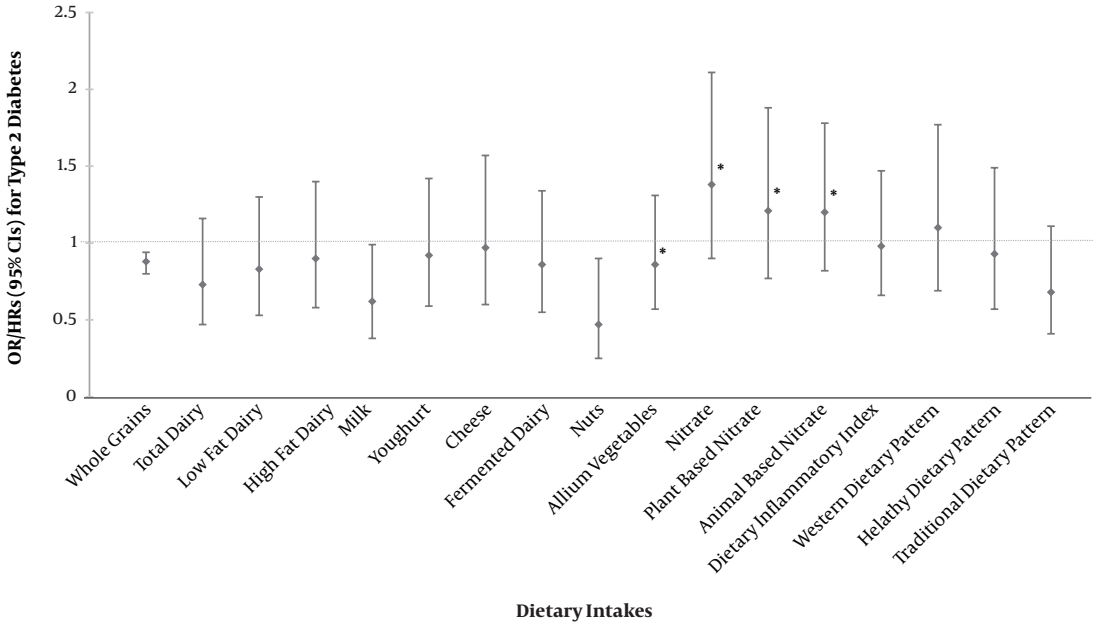

Figure 1. Risk of type 2 diabetes in individuals with highest vs. lowest categories of dietary parameters: Tehran Lipid and Glucose Study. *Presented as HRs (95%CIs). HRs, hazard ratios; ORs, odds ratios; CIs, confidence intervals.

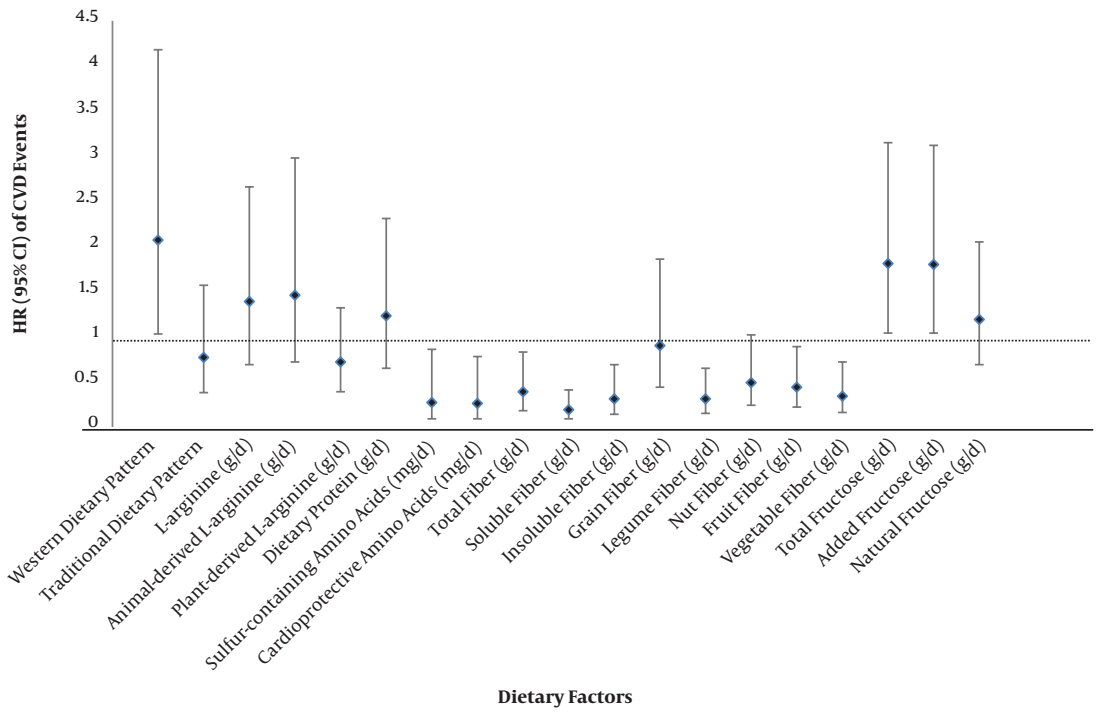

Figure 2. Risk of cardiovascular disease (CVD) in individuals with highest vs. lowest categories of dietary parameters: Tehran Lipid and Glucose Study. HRs, hazard ratios.

- 1.79) after adjustment for confounders. However, carbohydrate, simple sugar, fructose, total fat, SFAs, MUFAs, and $\omega 3$ fatty acids did not show any significant findings (51). In a 3-year longitudinal analyses, individuals in the top quintile of folate (OR: 0.44, 95% CI: 0.24 - 0.80), cobalamin (OR: 0.57, 95% CI: 0.34 - 0.93), vitamin C (OR: 0.38, 95% CI: 0.21 - 0.69), vitamin E (OR: 0.45, 95% CI: 0.22 - 0.92), vitamin D (OR: 0.39, 95% CI: 0.21 - 0.70), potassium (OR: 0.47, 95% CI: 0.23 - 0.97) and magnesium (OR: 0.41, 95% CI: 0.22 - 0.76) had decreased risk of CKD, and those in the highest quintile of sodium (OR: 1.64, 95% CI: 1.03 - 2.61), subjects had increased risk of CKD, in comparison to the lowest quintile in the fully adjusted model. No significant associations were found between the intakes of thiamin, riboflavin, niacin, pyridoxine, vitamin A, calcium, phosphorus, selenium, and zinc (52). From a holistic point of view, emphasizing high consumption of vitamins C, D, E, B12, and potassium, folate, and magnesium and low intake of sodium, predominantly found in fruits, vegetables, dairy foods, whole grains, legumes, nuts, and fish can decrease the risk of incidence CKD. This point has been supported by studies indicating that micronutrient-rich DPs lead to promoting the kidney function, thereby decreasing risk of renal failure. In two longitudinal studies conducted within the framework of TLGS, subjects in the highest quartile of the MDS were 51% less likely to have CKD than those in the lowest quartile (OR: 0.49; 95% CI: 0.30 - 0.82) after adjustment for all potential confounding variables. The inverse relationship between the MDS and the 6-year incidence of CKD remained significant (OR: 0.53; 95% CI: 0.31 - 0.91) after further adjustment for baseline eGFR (53). Furthermore, the OR for participants in the highest, compared with the lowest quintile of the DASH-style diet was 0.41 (95% CI: 0.24 - 0.70) after adjustment for age, sex, smoking, total energy intake, BMI, eGFR, triglycerides, physical activity, hypertension and T2DM (8).

Regarding food groups, in a cross-sectional study, compared to participants taking < 0.5 serving/week, consumption of over four servings of sugar sweetened beverages (SSBs) and sugar sweetened carbonated soft drinks (SSSDs) per week was related to increased OR of prevalent CKD (1.77 and 2.14, respectively). In a longitudinal analysis, risk of incident CKD increased by consumption of four servings/week, compared to less than 0.5 serving/week of SSBs (OR: 1.96, 95% CI: 1.23 - 3.15) and SSSDs (OR: 2.45, 95% CI: 1.55 - 3.89) (55). In a cross-sectional study higher risk (OR: 1.48, 95% CI: 1.05 - 2.13) of CKD was found comparing the highest tertile to the lowest one of nitrate-containing vegetables (NCVs); however, after 3 years of follow-up, there was no significant association between consumption of total NCVs and its categories with the occurrence of CKD (54). In a 6-year longitudinal analysis, the highest, compared to the lowest tertile of dietary nitrite was accompanied with a reduced risk of CKD (OR: 0.50, 95% CI: 0.24 - 0.89). However, dietary intake of nitrate had no significant association with the risk of CKD (57). In a cross-sectional analysis, the OR (95% CI) of CKD in the highest, compared to the lowest quartile of potential renal acid load (PRAL) of dietary intakes was 1.38 (95% CI: 1.02 - 1.83) after adjustment for age, sex, and body mass index. The positive association of PRAL and risk of CKD remained significant (OR: 1.42; 95% CI: 1.06 - 1.91) after additional adjustment for energy intake, smoking, dietary intake of total fat, carbohydrate, dietary fiber, fructose, sodium, T2DM, and hypertension (11). In a 3-year longitudinal analyses, compared to the first quartile of dietary AGEs intakes from fat, participants of the fourth quartile had higher risk of CKD (OR: 2.02; 95% CI: 1.16 - 3.54); the association between AGE intakes from meat and CKD was not statistically significant (55). In a 6-year longitudinal analyses, a higher habitual intake of allium vegetables was related to 32% lower incidence of CKD (hazard ratio: 0.68; 95% CI: 0.46 - 0.98; P for trend < 0.11) in a multivariable-adjusted model (1).

Overall, the results of our previous investigations suggest that higher intakes of dietary nitrate, MDS and DASH style DP, allium vegetables, and micro- and macronutrients such as vitamins C, E, D, B12, folate, potassium, magnesium, plant protein, PUFA, and $\omega 6$ fatty acid, decrease risk of CKD, whereas higher intakes of sodium, animal protein, SSBs, SSSDs, dietary acid load, and advanced glycation end-products were related to increased risk of CKD, findings showed that dietary sources of renal-protective nutrients should be emphasized among the general population (Figure 3).

4. Conclusions

Dietary patterns of most Tehranian adults need improvement. The FFQ is an acceptable tool for estimation of nutrient and food group intakes and determining DPs of Iranians to study association between DPs and health outcomes in epidemiological studies.

Some micro- and macronutrients, healthy DPs and allium vegetables were dietary sources of renal-protective nutrients. Higher adherence to healthy food choices were associated with reduced odds of dysglycemia and CVD.

It is recommended to investigate time trends of conforming dietary factors in accordance with dietary guide-

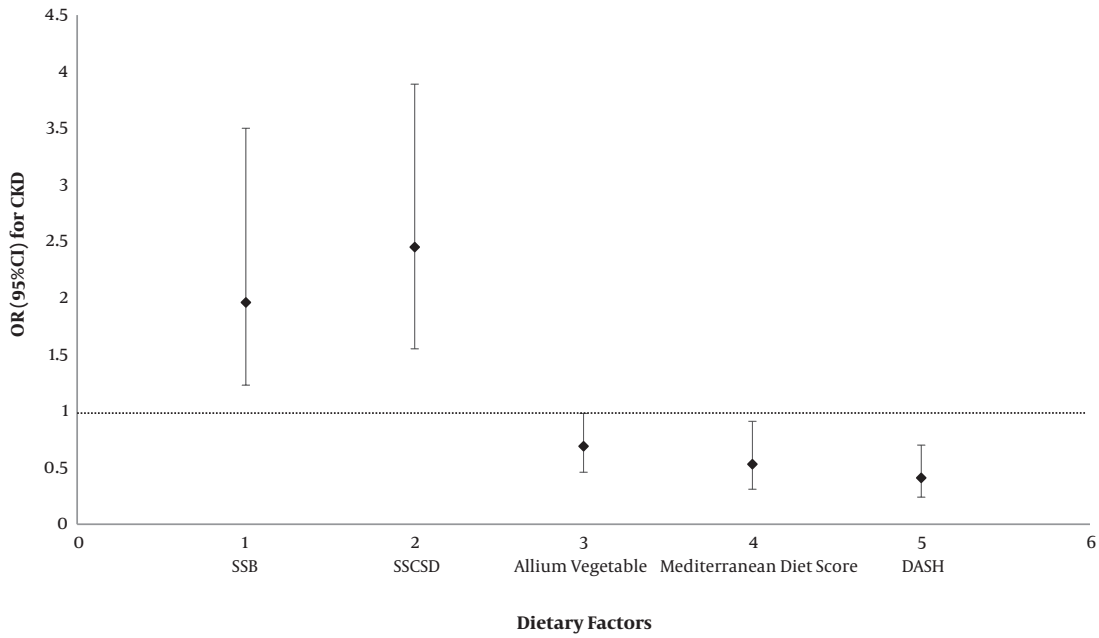

Figure 3. Risk of chronic kidney disease (CKD) in individuals with highest vs. lowest categories of dietary parameters: Tehran Lipid and Glucose Study. ORs, odds ratios; CIs, confidence intervals; SSB, sugar sweetened beverage; SSCSD, sugar sweetened carbonated soft drinks; DASH, dietary approaches to stop hypertension.

lines and their relations to T2DM, CVD and CKD to ensure precious dietary recommendations.

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Footnotes

Authors' Contribution: Firoozeh Hosseini-Esfahani, Nazanin Moslehi, Golaleh Asghari, Somayeh Hosseinpour-Niazi, Zahra Bahadoran, Emad Yuzbashian, designed the study and interpreted the data, and drafting the manuscript; Fereidoun Azizi and Parvin Mirmiran supervised the study, Fereidoun Azizi critically revised the manuscript for important intellectual content and final approval of the version to be published.

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Nutrition and Cardio-Metabolic Risk Factors: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: Genetic and environmental factors contribute to the incidence of metabolic syndrome (MetS). This study aimed to review all findings of studies conducted in framework of the Tehran lipid and glucose study (TLGS) regarding the association of dietary factors with cardio-metabolic risk factors.

Evidence Acquisition: All English-language studies were searched using PubMed and Scopus databases from 2000 to 2017. Finally, 105 relevant papers were included in this review.

Results: Whole grains, legumes, nuts and healthy dietary patterns (DPs) reduced risk of MetS, while white rice, salty/sweet snacks increased this. The western DP had a significant interaction with APOC3, APOA1 and MC4R polymorphisms in relation to MetS. After 6.5 years of follow-up, odds of reaching menarche $\leq$ 12 years was significantly higher in girls with higher intakes of milk, calcium, magnesium, and phosphorous. Among children and adolescents, higher adherence to the dietary approaches to stop hypertension (DASH)-style diet decreased the risk of abdominal obesity, whereas increased adherence to the western DP could contribute to general and abdominal obesity. A three-year follow-up of adult participants showed that higher intakes of phytochemical-rich foods were inversely related to development of insulin resistance. Higher adherence to the healthy DPs was associated with the reduced risk of hyperlipidemia and hypertention. Nutrition interventions postponed rise in the prevalence of MetS. The DASH diet resulted in weight reduction compared to control diet.

Conclusions: Higher adherence to healthy food choices was associated with reduced odds of MetS, abdominal obesity, dyslipidemia and hypertension. The western DP accentuated the association of polymorphisms with MetS.

Keywords: Cardiovascular Risk Factors, Diet, Nutrients, Tehran Lipid and Glucose Study, Metabolic Syndrome

1. Context

Metabolic syndrome (MetS), is a complex metabolic disorder including abdominal obesity, impaired glucose homeostasis, dyslipidemia, and hypertension, all of which can lead to cardiovascular disease (CVD) and diabetes; its prevalence is fast increasing over the last two decades (1-4). Genetics, sedentary lifestyles and nutrition transition with an accelerating tendency to a westernized diet are considered important factors contributing to the incidence of MetS (5-7). Fast foods with high energy density and higher amounts of fat, saturated fatty acids (SFA) and sodium along with carbonated soft drinks lead to weight gain and increased prevalence of cardio-metabolic risk factors (2, 8, 9). Also increasing fast food consumption is associated with lower diet quality (9). Higher intakes of fiber and phytochemical rich foods including fruits and vegetables, legumes, nuts and whole grains are related to lower risk of cardio-metabolic risk factors (10). Understanding the overall effects of diets through extracting and defining dietary patterns (DPs) elucidates associations of dietary factors and cardiovascular risk factors (11). The Mediterranean diet (Med) and dietary approach to stop hypertension (DASH) style diet, as models of healthy patterns, have been proposed to play a favorable role in the prevention of CVD (1, 7).

Individuals however are not affected equally by un-

healthy DPs, some being more sensitive to the harmful effects than others. This heterogeneity may reflect complex interactions between genetic susceptibilities and environmental factors, particularly diet in which some dietary factors modulate the association of polymorphisms and MetS, emphasizing the importance of gene-diet interaction studies (3, 5, 12).

Tehran lipid and glucose study (TLGS) is an ongoing study initiated in 1999 with a representative sample of 15005 individuals aged $\geq$ 3 years, recruited from among residents of district 13 of Tehran, the capital of Iran (13). This prospective study provides an opportunity to study different aspects of cardio-metabolic risk factors in this Middle-Eastern population. The aim of this study was to review all findings of studies conducted within the framework of the TLGS regarding the association of dietary factors (nutrients, food groups and dietary patterns) with cardio-metabolic risk factors, MetS and its components in different age groups.

2. Methods

All English-language studies, from 2000 to 2017, investigating cross-sectional or prospective associations of dietary patterns or food components with development of metabolic disorders in the framework of the TLGS, were searched using PubMed, Scopus, and Embase databases. A structured search strategy using a combination of keywords (diet, nutrition, metabolic syndrome, obesity, insulin resistance, lipids, blood pressure, hypertension, Tehran lipid and glucose study) were conducted to identify records in each database. Nutrigenetic studies conducted in the TLGS were also searched using combination of following key words: Diet, nutrition, gene or polymorphism, Tehran lipid and glucose study. Furthermore, studies focusing on polycystic ovary syndrome and other metabolic disorders in women were also included in this systematic review. Finally, 105 relevant papers were included in this review; 51 papers described the association of dietary factors with the risk of MetS and its components. Associations of nutrition and obesity were described in 58 papers; potential effects of diet and development of insulin resistance were explained in 7 articles, and three focused on nutrition and women's health. Interactions of dietary factors with common polymorphisms of obesity, dyslipidemia and MetS in TLGS population were investigated in 4 papers.

2.1. Nutrition and Metabolic Syndrome

2.1.1. Food Groups

Dairy consumption was associated with 18% reduced risk of MetS in adults (14), although these products did not reduce the risk in adolescents (15). Whole-grain consumption reduced risk of MetS by 32% in adults (16). Legume consumption more than 3 servings per week reduced risk of MetS by 32% (17). Nuts and dried fruits consumed > 15.5 g/d reduced the risk of MetS by 35% in adolescents (18).

Fast food consumption had undesirable effects on MetS. The associations of fast food consumption with the occurrence of MetS were more pronounced in younger adults (< 30 years) (2). White rice had undesirable effects on the incidence of MetS (19). Energy-dense nutrient-poor solid snacks (both salty and sweet) and sugar sweetened beverages (SSB) were associated with a > 50% increased incidence of MetS in children, adolescents and adults (Figure 1) (20-23).

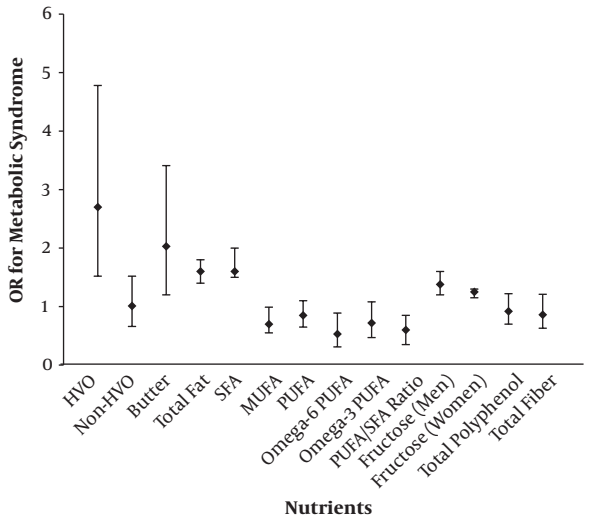

Figure 1. The association of dietary nutrients and metabolic syndrome: Tehran lipid and glucose study. Odds ratios (ORs) were estimated for highest category vs lowest category by adjusted logistic regression analysis. Abbreviations: HVO, hydrogenated vegetable oil; MUFA, Mono-unsaturated fatty acids; PUFA, poly-unsaturated fatty acids; SFA, saturated fatty acids.

2.1.2. Nutrients

Low carbohydrate diet (LCD) scores were associated with a decreased risk of MetS in adults (24), although this score had no association with incidence of MetS in children and adolescents (25). Total dietary fiber, soluble- and insoluble fiber, fruit fiber, cereal fiber and legume fiber were negatively associated with MetS (26). Higher intake of magnesium consumption reduced risk of MetS in obese participants (β = -0.014, P < 0.05) (27). Subclasses of polyphenols such as flavonoids were associated with a lower prevalence of MetS among adults (OR: 0.25, CI: 0.19 - 0.34 in highest vs lowest category) (28). Alpha-linolenic acid (ALA) consumption was inversely associated with the

MetS, irrespective of the background consumption of n-6 poly-unsaturated fatty acids (PUFAs) in adults (29). Dietary antioxidants had favorable effects on metabolic disorders (30).

Fructose had an association with increased risk of MetS in adults (31). Total fat, especially saturated fat (SFA), Hydrogenated vegetable oils and butter were associated with a higher risk of MetS in adults (32, 33). Fatty acids, except PUFA and MUFA consumption, increased the risk of MetS (34); SFA consumption was positively associated with the prevalence of MetS, independent of total dietary fat, MUFA and PUFA consumption (Figure 2) (4).

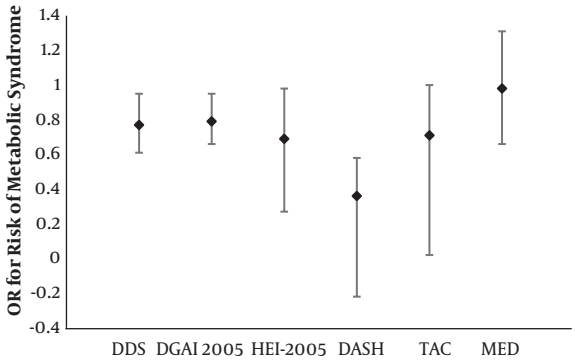

Figure 2. The association of different dietary patterns and metabolic syndrome: Tehran lipid and glucose study. Odds ratios (ORs) were estimated for highest category vs lowest category by adjusted logistic regression analysis. Abbreviations: DASH, dietary approach to stop hypertension; DDS, dietary diversity score; DGAI 2005, dietary guidelines for Americans adherence index 2005; HEI-2005, healthy eating index, MED, mediterranean diet; TAC, total antioxidant capacity.

2.1.3. Dietary Patterns

Higher adherence to DASH diet and the dietary guidelines for Americans adherence index (DGAI)-2005 reduced risk of MetS (1, 35, 36). Mediterranean diet score (MDS) was not associated with MetS incidence (7). Dietary diversity score (DDS) had an inverse association with MetS. (37). Whole grains, multiple types of vegetables and fruits, yoghurt and ice cream had protective effects against MetS (38). Adherence to common nutritional targets of public health (total fat, SFA, fiber, fruit and vegetable) had inversely associated with MetS risk factors in Tehranian adults (39). Increased fat consumption and overall unhealthy dietary patterns were associated with MetS (Figure 3) (40).

2.2. Nutritional Intervention

Nutrition interventions based on the therapeutic lifestyle change diet guidelines did not reduce the risk of MetS (41), although they did delay the rise in the prevalence of MetS and some of its components (42).

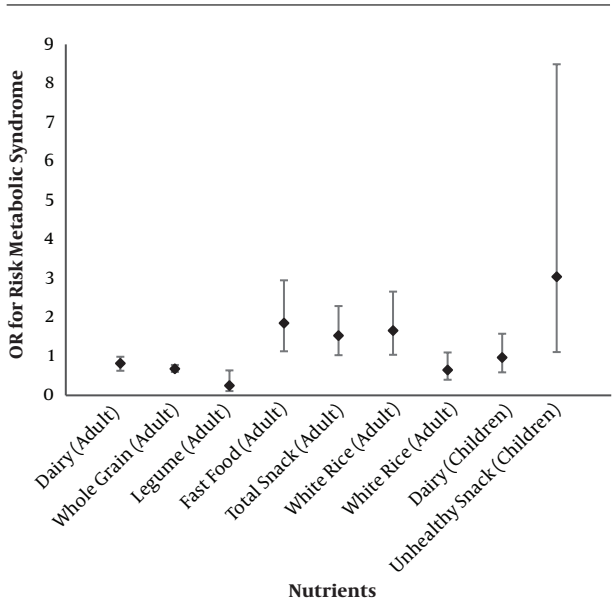

Figure 3. The association of different food group intake and metabolic syndrome: Tehran lipid and glucose study. Odds ratios (ORs) were estimated for highest category vs lowest category by adjusted logistic regression analysis.

2.3. Nutrigenetic Studies

The interaction between genetic susceptibilities and dietary factors plays an important role in diet-related polygenic disorders, such as MetS. Western DP scores (loaded heavily on fast food, soft drinks and salty snacks) had a significant interaction with the APOC3 3238C>G and APOA1 (rs670, -75G>A and rs5069+83C>T) polymorphisms in relation to risk of MetS (11). Compared with other genotype combinations, the combined effect of APOC3/APOA1 (CC/GA+AA/CT+TT) genotypes showed a further increase in the risk of the MetS in the highest quartile of western DP scores (5).

Among A allele carriers (GA+AA) of MC4R rs12970134, being in the highest quartiles of the western DP score and SFA intake had an increased risk of MetS, compared to those in the lowest quartile (12). A significant interaction was observed between rs12970134 with total fat and iron intake on the risk of abdominal obesity. Moreover there are interactions between omega-3 fatty acids, zinc, salty snacks and ZNT8 variant rs13266634, which may affect the risk of MetS or its components (3).

2.4. Nutrition and Women's Health

Timing of menarche occurrence is important because it can affect women's health and reproduction; age at menarche was significantly higher in underweight girls (14.4 $\pm$ 1.1) than normal weight (13 $\pm$ 1.2), overweight (12.8

$\pm$ 1.3) and obese (12.8 $\pm$ 1.2) ones. BMI and age at menarche were negatively correlated (r = -0.13, P = 0.012) (43).

A prospective study investigated the association between dairy intakes and timing of menarche among 134 pre-pubertal girls, aged 4 - 12 years. After 6.5 years of follow-up, odds of reaching menarche $\leq$ 12 years was significantly higher in girls with higher intakes of milk (OR = 2.25, 95% CI: 1.03 - 5.05), calcium (OR = 3.20, 95% CI: 1.39 - 7.42), magnesium (OR = 2.43, 95% CI: 1.12 - 5.27), and phosphorous (OR = 3.37, 95% CI: 1.44 - 7.87) (44).

Associations between the visceral adiposity index (VAI) DP and cardio-metabolic variables were examined in 53 polycystic ovary syndrome (PCOS) subjects and 167 age-matched non-PCOS women. Higher adherence to the pattern was associated with higher triglycerides, the triglycerides/high density lipoprotein cholesterol (HDL-C) ratio and higher odds of visceral adiposity dysfunction. In non-PCOS women with more adherence to the pattern, the odds of hypercholesterolemia, high low density lipoprotein cholesterol (LDL-C), low HDL-C, hyperglycemia and impaired glucose tolerance (IGT)+impaired fasting glucose (IFG) were also higher (45).

Data on a later age at menarche in underweight children with no significant differences in age at menarche between overweight and obese children (43) indicates that BMI is a determinant of menarche although it seems that the association between BMI and menarche may not be linear. The observation of higher risk of early menarche with higher intakes of milk during childhood, (but not cheese and yoghurt) can partly be explained with insulin like growth factor 1 (IGF-1) secretion. Stimulation of IGF-1 secretion by bioactive components of milk, i.e. dairy protein, calcium, magnesium, phosphorus increases estrogen production through stimulating adrenal androgen secretion or gonadotropin-releasing hormone (GnRH) by hypothalamic neurons; these bioactive components may be inactive during the processing of milk (44).

2.5. Nutrition and Obesity

2.5.1. Food Groups

Higher dairy consumption in the TLGS study, both cross-sectional (46) and cohort (14) designs had inverse associations with waist circumference (WC) and obesity in adults. Dairy intake generally showed controversial findings as supported by systematic reviews and meta-analyses. Excessive consumption of high-calorie foods, including sweet drinks and SSB was accompanied with increased risk of overweight and abdominal obesity in two cross-sectional studies in adult participants of the TLGS (21, 47), a finding confirmed by most previous studies, in particularly recent systematic reviews that documented a positive association between SSB consumption and obesity indices in children and adults. Findings of these researches lead to exerting tax on SSBs for reducing obesity and chronic diseases.

Dietary intakes of whole grains and vegetables as a part of healthy diet, indicated an association with weight control; in a cross-sectional analysis, adults with higher intakes of whole grain had 10% lower risk of enlarged WC (16). Similarly, alterations in the consumption of whole grains, vegetables, and added sugars were associated with body weight change, suggesting the effect of food choices on weight control (48). Whereas higher intakes of hydrogenated vegetable oils and advanced glycation end (AGE) products, identified as a part of unhealthy diets are accompanied with increased risk of abdominal obesity (33, 49).

Fast foods, which have high energy densities and glycemic loads, could contribute to overweight and obesity. However, in adults no significant difference between 3-year changes of weight with quartile categories of fast food consumption was observed, which may be justified by a wide age of participants (19 - 70 years) and a short follow up (3 years) in the study (2). Notably, refined grains (16), legumes (17), fast foods (2), snacks (20), and rice (19) showed no significant association with risk of abdominal obesity or WC values. It is noteworthy that generally these foods had an association with MetS and other chronic diseases, not just weight gain.

Like most other cohorts, among children and adolescents in the TLGS, higher intakes of SSB (OR: 2.49; 95% CI: 1.00 - 6.53) (23), and fast food (OR: 2.58; 95% CI: 1.01 - 6.61; P for trend = 0.009) (8) had increased risk of abdominal obesity. This may be justified by high preference for increased intakes of SSBs and fast food in childhood; fast foods encompass higher percentage of total calorie intake in youth compared to adults. However, no significant relationship was found for abdominal obesity with intakes of dairy (15), energy-dense nutrient-poor solid snacks (22), nuts and dried fruits (50); It seems that children are less tempted to consume dairy, nuts and dried fruits and these foods do not highly contribute to their daily calorie intake.

2.5.2. Nutrients

The relationship between macronutrient intakes and body mass index in a group of the TLGS participants was assessed and energy from fat was found to be independently and positively associated with obesity; contradictory to this result, energy from protein and carbohydrate had no association with BMI (51), a finding mostly consistent with results of large population based studies justified by the fact that higher intakes of fat lead to weight gain. However, differences in amounts of protein intakes had a narrow range.

Cohort studies examined the association of different nutrients, viz. simple sugars (fructose), various types of saturated and unsaturated fats, minerals (calcium and magnesium and some phytochemicals) with overweight and obesity; these studies may provide both consistent or contradictory findings based on the differentiation in study design, population sample size, and other demographic features. In a cross-sectional analysis, TLGS participants with higher intakes of magnesium (β = -0.013, P = 0.006) (27), ω-3 PUFA (OR: 0.52; 95% CI: 0.35 - 0.75; P trend = 0.014), ALA (OR: 0.54; 95% CI: 0.37 - 0.80; P trend = 0.003) (29), total antioxidant capacity (OR: 0.62; 95% CI: 0.38 - 0.99; P trend = 0.01) (30), flavonoid (OR: 0.31; 95% CI: 0.23 - 0.40; P trend < 0.005) (28), total fiber (89.4 cm vs 91.8 cm) (26), had lower risk of having enlarged WC. Higher intake of fructose (39 in men and 20% in women) (31), higher ω-6/ω-3 ratio (OR: 1.51; 95% CI: 1.14 - 2.00; P trend = 0.003) (29), and combined effect of total fat and SFA (OR: 1.37; 95% CI: 1.02 - 1.83) (4) were accompanied with increased risk of abdominal obesity. Fatty acid composition (32, 34), total polyphenol, phenolic acid, stilbene, lignan (28), combined effect of MUFA and SFA and combined effects of PUFA and SFA (4), showed no significant associations with risk of abdominal obesity or WC values.

2.5.3. Dietary Patterns

Today, a method commonly used in cohort studies worldwide for evaluation of diet-chronic disease associations is DPs approach, priori or posteriori. The TLGS study aimed to demonstrate the main DPs in an appropriate population sample of Iranians of various demographic subgroups and investigated the association of these patterns with weight changes and obesity. All obesity indices had an increasing trend across quintiles of the traditional DP, which is rich in refined carbohydrates, whole grain, starchy vegetables, other vegetables, red and refined meat, saturated/trans-fat, and egg (52); furthermore, increased adherence to the western DP contributed to general and abdominal obesity (53). However, DDS (37), DGAI-2005 (36), or the Med diet (23) showed no significant association with risk of abdominal obesity or WC values.

In adolescents, BMI was negatively related with breakfast energy percentage in girls (r = -0.18, P < 0.01) and positively related with lunch energy percentage in both sexes (r = 0.16, P < 0.05 in boys and r = 0.22, P < 0.01 in girls) (54). Moreover, evaluation of the relationship between diet quality scores HEI-2005 and HEI-2010, with risk of obesity in Tehranian adolescents revealed that participants in the highest quartile of HEI-2010 compared to those in the lowest had lower risk of general and central obesity (55); however, these indices were not successful in predicting BMI and WC in Iranian adults after 6.7 years of follow-up (56). No significant relationship of HEI-2005 score (57) and LCD score (25) with abdominal obesity was found among children and adolescents; however, higher adherence to DASH-style diet decreased the risk of abdominal obesity (OR: 0.35; 95% CI: 0.14 - 0.89; P trend = 0.047) (1).

Intakes of phytochemical-rich foods, high dietary phytochemical index, and the total antioxidant capacity diet had favorable effects on prevention of weight gain (30, 58). There was a significant association of LCD score with WC-BMI (β = -0.003, 95% CI: -0.005, -0.001) (24).

2.5.4. Nutrition Intervention

In addition to these results, community based lifestyle modifications in Tehranian adults were also effective on the prevalence of abdominal obesity (42). Of course, regarding gender differences in the mean daily intakes of energy and nutrients, these behavioral interventions and nutritional recommendations should be targeted and gender-specific (59). The DASH diet resulted in weight reduction among men (-16 and -14 kg) and women (-16 and -15 kg) in comparison to the control diet (35). The educational nutrition program had no effects on obesity and abdominal obesity (41). Moreover, a familial obesity pattern was observed in the TLGS population; therefore, familial interventions seem essential to combat obesity in Iran (60).

In summary, whole grains, dairy, fruits, vegetables, phytochemical-rich foods in the framework of a healthy DP are found to be associated with general and abdominal obesity in children, adolescents, and adults. However, some controversies may exist with previous cohort studies; highlighting the need for more investigations in subgroup analyses and longer follow-up durations.

2.6. Nutrition and Insulin Resistance

A three-year follow-up of adult participants showed that higher intakes of phytochemical-rich foods (OR = 0.48, 95% CI = 0.25 - 0.93), in the last compared to the first quartile, dietary intakes of β-carotene (OR = 0.42, 95% CI = 0.25 - 0.72) and β-cryptoxanthin (OR = 0.51, 95% CI = 0.30 - 0.84) were inversely related to development of insulin resistance (IR) (61, 62). Healthy DP (characterized by higher load of vegetables, fresh and dried fruits, low-fat dairy, vegetable oils, nuts and seeds) score was negatively related to 3-year changes in fasting serum insulin (β = -4.91, 95% CI = -9.47, -0.39) and IR index (β=-5.99, 95% CI = -11.7, -0.23) (63); compared to the lowest tertile of healthy pattern score, the highest was accompanied with an 81% reduced risk of IR (OR = 0.19, 95% CI = 0.10 - 0.36) (64). Dietary inflammatory index was not significantly related to risk of IR in our population (65), whereas potential renal acid load (OR = 2.81, 95% CI = 1.32 - 5.97) and net endogenous acid production score

(OR = 2.18, 95% CI = 1.03 - 4.61) were positively related to development of IR (66); compared to the lowest, the highest tertile of dietary insulin load was also significantly associated with increased risk of IR (OR = 1.69, 95% CI = 1.01 - 2.89) (67).

Several dietary indicators, e.g. phytochemical index, healthy dietary pattern score, renal acid load, and insulin load have been identified to be potential factors, which could affect development of IR in the TLGS population.

2.7. Nutrition and Dyslipidemia

2.7.1. Food Groups

Participants in the highest quartile of whole-grain intake had a significantly lower prevalence of hypertriglyceridemic waist phenotype (22%) than those in the lowest quartile. Conversely, those in the highest quartile of refined-grain intake had a significantly higher prevalence (2-fold) of the hypertriglyceridemic waist phenotype than did those in the lowest quartile (68). The odds of prevalent hypertriglyceridemia (total cholesterol $\geq$ 240 mg/dL) for participants in the highest quartile of whole grains compared to those in the lowest, was 0.61. Furthermore, subjects in the highest quartile of refined-grain intake had higher chances of being hypercholestrolemic, hypertriglyceridemic, and having high LDL-C. A significant decreasing trend was observed among participants in the top quartile of whole-grain intake for having high-serum triglyceride levels, similar to subjects in the upper quartile of refined-grain intake, who had also higher chances of having high-serum triglyceride levels (triglycerides $\geq$ 150 mg/dL) (16). A significant increasing trend was observed for prevalence of high triglyceride concentrations across quartiles of dairy products (14). In another study, multivariate-adjusted odds ratios for the high total cholesterol and high LDL-C across quartiles of fruit and vegetable intakes were 0.82 and 0.79, respectively (69). Fast food consumption had a positive association with serum triglycerides and negative association HDL-C in middle-aged adults (31 - 51 years) (9). The odds of prevalent low HDL-C had increasing trends across increasing categories of SSB consumption (21). Among men, total intakes of fruit and vegetables were inversely associated with 3-year changes in triglycerides and total cholesterol. Yellow fruits and vegetables were inversely associated with 3-year changes of total cholesterol and HDL-C. Dietary intakes of green fruit and vegetable were inversely associated with triglycerides levels and triglycerides/HDL-C ratio. Moreover, white fruit and vegetable intakes were related to lower abdominal fat gain and inversely associated with total cholesterol changes. Among women, higher consumption of red/purple fruit and vegetable was inversely related to 3-year changes of total cholesterol. Consumption of orange fruits and vegetables had significant inverse associations with 3-year changes of total cholesterol (70). Higher intake of hydrogenated vegetable oils was positively associated with 3-year changes of serum triglycerides. Furthermore, intake of butter was positively associated with serum triglycerides and negatively associated with HDL-C levels (33). A negative association was observed between allium vegetable intakes and 6 year changes of triglyceride levels (71).

2.7.2. Nutrients

There were no significant differences in low HDL-C across dietary fructose quartiles in men and women (31). Findings of another study showed that participants in the highest quartile of fat consumption had increased odds of having high serum triglycerides (40). Serum total cholesterol and HDL-C were increased in participants with higher intake of SFA (32, 72). Intakes of ω-3 PUFA, eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA), and ALA were inversely associated with high serum triacylglycerol concentrations. In addition, a higher EPA+DHA intake was associated with a 34% lower concentration of high serum triacylglycerol in participants with a lower ω-6 PUFA intake and a 28% lower concentration in subjects with a higher ω-6 PUFA intake, compared to those with lower EPA+DHA intake (29). Serum LDL-C and triglyceride levels were positively associated with SFA intake, whereas LDL-C was inversely associated with mono-unsaturated fatty acid (MUFA). HDL-C level was inversely associated with SFA and PUFA intake and the positive association with MUFA and the ratio of PUFA to SFA. The LDL/HDL-C ratio was negatively associated with the ratio of PUFA to SFA ratio (34). A combination of high SFA intake and low MUFA intake was associated with high serum triglyceride concentrations (4). Serum HDL-C was associated with total protein intake in men and women (73). Dietary magnesium was inversely associated with serum triglycerides, while copper intake was positively associated with HDL-C (27, 74). Dietary total antioxidant capacity were negatively associated with triglycerides, and positively associated with HDL-C levels (30). Those in highest quartile of dietary flavonoid intakes had 65% lower risk of hypertriglyceridemia and 33% lower risk of low HDL-C, compared to those in the lowest quartile. In addition, subjects in the highest quartile of dietary lignan intakes had higher odds of (33%) having hypertriglyceridemia (28). Dietary potential renal acid load was associated with serum triglycerides, HDL-C. In addition, protein to potassium ratio was associated with serum HDL-C and triglycerides (75). The highest quartile of protein intake was inversely associated with 3-year changes in total cholesterol and HDL-C levels in men, compared to

the lowest quartile. Dietary protein to carbohydrate ratio in men was associated with 3-year changes in serum triglycerides and total cholesterol. In women, dietary protein and protein to carbohydrate ratio showed no significant relation with lipid profile changes (76). Participants in the highest compared to the lowest quartile of dietary fiber and phytochemical-rich foods decreased risk of incident hypertriglyceridemia by 42% after 3 years of follow-up. In addition, higher dietary sodium to potassium ratios compared to lower ratios increased the risk of hypertriglyceridemia by 63% (77). Med score was not associated with components of MetS (23). There was no significant association between serum nitric-oxide (NOx) and the incidence of hypertriglyceridemic-waist in men; however, serum NOx in women increased by 46% the risk of incident hypertriglyceridemic-waist (78).

2.7.3. Dietary Patterns

Higher adherence to the DGAI was associated with a 31% decreased risk of low HDL-C prevalence (36). Participants in highest quartile of DDS, compared with those in the lowest ones had 16% lower risk of high serum triglycerides (37). The risk of having hypertriglyceridaemia decreased with increasing quartiles of the diversity score for whole grains. The odds of having hypercholesterolaemia and high LDL-C decreased with increasing quartiles of the diversity score for vegetables. The probability of having hypercholesterolaemia and high LDL-C decreased with quartiles of the DDS (79). Men in the highest quartile of the HEI-2005 score had significantly lower triglyceride changes than those in the lowest quartile, although, there was no such relation in women (80). LCD score was negatively associated with triglycerides among adults (24). There were positive correlations between dietary carbohydrate and serum triglycerides, cholesterol intake and serum LDL-C (81). Higher dietary glycemic index was associated with higher triglyceride concentrations and lower HDL-C among obese individuals (BMI > 30) (82). Compared with those in the upper quartiles, participants in the lower quartile of dietary phytochemical index had a 36% lower risk of elevated serum triglycerides (10). Dietary intakes of AGE products were not associated with prevalence of high triglycerides and low HDL-C (49).

An inverse association was observed between dietary phytochemical index and 3 years changes of total cholesterol, triglycerides, HDL-C, and non-HDL-C in men, while this index had no association in women (83). In addition, risk for incidence of hypertriglyceridemic waist phenotype in participants with the highest compared to the lowest dietary phytochemical index was significantly reduced (84). Higher adherence to the traditional DP score was associated with changes in HDL-C level during 4.7 years of follow-up. However, there was no significant association between western DP scores and changes in serum HDL-C (85).

2.7.4. Nutrition and Dyslipidemia in Children and Adolescents

Adolescents in the highest HEI-2005 category had 38% lower odds of prevalence high triglycerides and 37% lower risk of low HDL-C compared with those in the lowest category (57). Among adolescents, serum triglycerides decreased with increasing the quartiles of energy intake from PUFA. Moreover, serum HDL-C level decreased according to the quartiles of percent of energy intake from PUFA (86). In adolescents aged 10 - 19 years, dietary intake of dairy products was not associated with prevalence of high triglycerides and low HDL-C (15). Among children and adolescents, aged 10 - 19 years the concentration of triglycerides significantly decreased across the quartiles of nuts and dried fruit intakes (50). Among adolescents those in the lowest quartile of LCD score, compared with those in the highest quartile had odds ratios of 0.55 and 0.49 in the incidence of high triglycerides and low HDL-C, respectively (25). Among children and adolescents aged 6 - 18 years, dietary intakes of SSBs had no association with high triglycerides and low HDL-C after 3 years of follow-up (23). Children and adolescents in highest quartile of fast food intake had a 2.8-fold higher risk of incident high triglycerides than those in the lowest intakes after 3 years of follow-up (8). After 3 years of follow-up in children and adolescents, higher adherence to the dietary approaches to stop hypertension style had no association with incidence of high triglycerides and low HDL-C (1). There was no significant association of dietary intakes of salty and sweetened snacks with incidence of high triglycerides and low HDL-C among children and adolescents after 3 years of follow-up (22).

To sum up, higher adherence to prudent DPs such as DGAI and HEI-2005 might improve dyslipidemia. In addition, increasing dietary diversity was associated with reduced hypercholesterolemia risk and decreased serum triglycerides. Besides, higher compliance with the LCD and dietary phytochemical index were associated with lower risk of hyperlipidemia. It seems that prudent dietary patterns have beneficial effects on lipid profiles due to high content of bioactive compounds, increased dietary diversity, and low dietary glycemic index.

Most of the studies have focused on the relationship between dietary fatty acids intake and dyslipidemia. Other food components such as magnesium, polyphenols, and fiber were also associated with dyslipidemia; this favorable effect on the lipid profile might pertain to the increased total anti-oxidant capacity and decreased dietary acid load, both of which had a significant association with lipid profile.

Adherence to the prudent dietary pattern such as HEI, DASH, and LCD might ameliorate or protect children and adolescents against dyslipidemia. Higher adherence to the healthy DP is associated with higher intakes of prudent foods, containing high amounts of antioxidants, magnesium, dietary fiber, fruits, and vegetables, all of which are beneficial for lipid hemostasis. Consumption of low glycemic index foods may improve insulin sensitivity and decrease cardiovascular risk factors in children and adolescents. The utility of diet quality indices in assessing eating behaviors of children and adolescents in relation to dyslipidemia may provide a valuable tool for monitoring and preventive strategies in public health education and intervention programs.

2.8. Nutrition and Hypertension

2.8.1. Food Groups

In a cross-sectional study on 827 adults, whole-grain consumption had a significant inverse association with high blood pressure (BP) (OR: 0.84, 95% CI: 0.73 - 0.99) (16). Subjects in the highest quartile of white rice intake had higher BP in compared to those in the lowest quartile of intake (19). Consumption of protein food groups had no association with the 3-year incidence of hypertension (87). In a case-control study of 240 adults, legume consumption reduced systolic but not diastolic BP (17). Consumption of dairy, high-fat dairy, non-fermented dairy and milk had inverse association with BP and hypertension in adults (14, 88) an association not observed in adolescents (15). In a prospective study conducted on 1087 adults, total dairy intake increased and decreased 3-year risk of hypertension incidence in men and women, respectively (89). Nuts, dried fruits and dietary magnesium showed non-significant association with BP (18, 27).

In two prospective studies, fast food consumption had no association with incidence of hypertension after a 3-year follow-up in both adolescents and adults (2, 8). There was no association between salty and sweet snacks and 3-year incidence of hypertension in adults (90); however, salty- but not sweet snacks had a significant inverse association with elevated BP in children and adolescents (22). SSB intake whether in children, adolescents or adults was associated with higher risk of elevated BP (21, 23). The highest tertile of nitrate-containing vegetables reduced 3-year incidence of hypertension by 37%, compared to the lowest tertile (91). Intakes of Allium vegetables had no relationship with risk of hypertension after a 6-year follow-up (71).

2.8.2. Nutrients

In an observational study, dietary fructose consumption showed a significant relationship with BP and systolic BP in men and women, respectively (31). Results of a cross-sectional study on 2537 adults showed that BP had no association with dietary protein intake and animal-to-plant protein ratio (73). In two cross-sectional studies, no relationships of BP with consumption of PUFA, MUFA, SFA, PUFA to SFA ratio, oleic acid and linoleic acid was found (32, 34). However, high dietary SFA increased risk of high BP independent of total fat and MUFA; on the contrary, high SFA among subjects with high PUFA intake decreased the risk of high BP by 9% (4). There was no significant association between hydrogenated, non-hydrogenated vegetable oils and butter and 3-year changes in systolic and diastolic BP (33). Dietary nitrite was inversely associated with 6-year risk of hypertension (OR: 0.58, 95% CI: 0.33 - 0.98) (92).

2.8.3. Dietary Patterns

The highest quartile of DDS was associated with 15% lower risk of high blood pressure (BP), compared to the lowest quartile of DDS (OR: 0.85, 95% CI: 0.58 - 1.13, P trend = 0.03) (37). DGAI-2005 was inversely associated with elevated BP (OR: 0.76, 95% CI: 0.70 - 0.93) (36). Healthy DP was inversely associated with systolic BP (OR: 0.74, 95% CI: 0.56 - 0.97) but not diastolic BP (93). There was no significant relationship between western DP and BP. In another study on 2241 adults (23), adherence to the Med diet had no association with 3-year changes in systolic BP and diastolic BP. In a cross-sectional study of 706 adolescents, HEI-2005 had no association with systolic- or diastolic BP (57). Asghari et al. (1) have indicated that compared to the lowest quartile of DASH, the highest quartile of DASH-style diet reduced 3-year risk of elevated BP by 30%. In a prospective study conducted on 2044 adults, LCD score had a negative association with high BP (β = -0.001, P = 0.04) after 3.6-years (24), although it had no relationship with BP in adolescents (25). In a cross-sectional study dietary phytochemical index showed no significant association with BP (10) although the highest quartile of this index was associated with the lower odds ratio 3-year incidence of hypertension (OR: 0.52, 95% CI: 0.32 - 0.84) (94). Dietary total antioxidant capacity and dietary flavonoid intake have a significant inverse association with elevated BP (28, 30). In a cross-sectional study (49), there was no relationship between AGEs products and elevated BP. Renal acid load (β = 0.06, P = 0.006) and protein to potassium ratio (β = 0.02, P = 0.04) were positively associated with diastolic BP, but not systolic BP (75).

2.8.4. Nutrition Intervention

Results of a longitudinal study reported that community-based education for lifestyle intervention had no effect on BP over a 3.6-year follow up (42).

Overall, whole grains, legumes, dairy and vegetables decreased risk of high BP, while fast foods and SSB elevated the risk of hypertension. Among nutrients high SFA intake increased risk of high BP, while dietary nitrite was inversely associated with risk of hypertension. Adherence to healthy DPs was inversely associated with high BP.

3. Conclusions

Some micro- and macronutrients, healthy DPs and healthy food groups were associated with reduced odds of cardio-metabolic risk factors. Unhealthy food groups like SSB and fast food increased cardiovascular risk factors. Unhealthy dietary patterns modified the association of polymorphisms with Mets.

It is recommended to investigate time trends of conforming dietary factors in accordance with dietary guidelines and their relations to MetS, abdominal obesity, dyslipidemia and hypertension for designing guidelines and implementing strategies aimed at disease prevention.

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Footnotes

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The Impact of Physical Activity on Non-communicable Diseases: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: Low physical activity is one of the major risk factors for non-communicable diseases (NCD) such as cardiovascular disease and type 2 diabetes. The current paper reviews the main findings from Tehran lipid and glucose study (TLGS) that focus on physical activity and its association with cardiometabolic risk factors over the past two decades.

Evidence Acquisition: We conducted a literature search for articles from 1999 to December 2017 using the search terms: (Physical activity, leisure time physical activity, non-communicable disease, and TLGS).

Results: The prevalence of low physical activity was 69.8% during phase II of TLGS (2000 - 2004). During 6.5 years of follow up, the prevalence of low physical activity in the total population decreased significantly between phases II (2000 - 2004) and IV of TLGS (2008 - 2010) ($P < 0.05$). Overweight individuals with sedentary lifestyles had a higher risk of metabolic syndrome, compared to those who had high levels of leisure-time physical activity in phase IV of TLGS (2008 - 2010); in the obese group, systolic blood pressure, and triglyceride levels differed significantly between different leisure-time physical activity categories (106.9 ± 14.3 vs. 119.1 ± 17.2 mmHg, $P = 0.03$) and (111.4 ± 1.6 vs. 147.1 ± 1.6 mg/dL, $P = 0.01$), respectively.

Conclusions: The present review highlights the impact of low physical activity on the health of the TLGS community from adolescence to adulthood. The decreased prevalence of low physical activity from phase II to phase IV of TLGS indicates the necessity for lifestyle interventions as a potentially effective strategy, which could have a positive impact on various risk factors and indicators of non-communicable diseases such as body mass index, waist circumference, systolic blood pressure, and lipid profiles.

Keywords: Low Physical Activity, Leisure-Time Physical Activity, Metabolic Syndrome, TLGS

1. Context

Low physical activity is one of the main risk factors for non-communicable diseases (NCDs) such as cardiovascular disease and type 2 diabetes (1, 2). The World Health Organization (WHO) reports that low physical activity causes 27% of diabetes and 20% of ischemic heart disease and it is one of the eight main risk factors of cardiovascular deaths, and, more importantly, is one of the five global risks for mortality (3). The health-care costs of low physical activity were estimated at $53.8 billion, including $5.0 billion for coronary heart disease and $37.5 billion for type 2 diabetes in 2013. Low physical activity is responsible for $2.4 billion health-care costs in the Eastern Mediterranean regions, with Iran's share estimated at $609,296 (4).

The Tehran lipid and glucose study (TLGS), a population-based study, has been designed with the aim of determining and preventing the risk factors for NCDs through changing lifestyles of the population since 1999. This study consists of two major components: Phase I is a cross-sectional prevalence study of NCDs and associated risk factors and phase II to VI are prospective interventional studies with repeated data collection every 3 years (5, 6). Data on TLGS physical activity was obtained using two questionnaires, the lipid research clinic (LRC) and modifiable activity questionnaire (MAQ). In addition, some efforts have been made to increase the rate of physical activity in the intervention phase of TLGS survey. These included; (1) face to face training, (2) physical activity training and emphasizing the importance of the sport education times in schools, (3) providing some facilities such as free or half-price vouchers for TLGS participants. The current paper hence reviews the main results of the studies investigating physical activity levels in the TLGS population.

2. Evidence Acquisition

We conducted a literature search for articles published between 1999 to December 2017 using the search terms: "physical activity", "leisure time physical activity", "non-communicable disease", and "TLGS" in PubMed database. Seventeen articles were found. During 20 years of TLGS, the impact of physical activity has been investigated in two forms; (1) as an independent and main risk factor for NCDs (2) as a dependent risk factor or confounder factor for other variables. Because of the importance of the first item and the extension of the second item, the current paper reviews the main results of the studies which targeted physical activity as the main risk factor in TLGS population.

Physical activity data were collected by two methods; LRC was used in initial phase of TLGS (phase I) and is a simple measure including four questions. Since the data obtained through LRC were rather subjective and not accurate for the Iranian culture, the physical activity questionnaire was replaced by a Persian-translated MAQ questioner, which measures leisure-time, job, and household activities and calculates the metabolic equivalent (MET) based on min/wk. 1500 min/wk) (7). The physical activity levels has been defined as low (MET < 600 min/wk), moderate (MET 600 - 1499 min/wk) and high (MET $\geq$ 1500 min/wk) levels (8). Momenan et al. have previously determined the reliability (98%) and validity (47%) of the Persian MAQ version (9). Leisure-time physical activity specifies performing three or more days of vigorous-intensity activity of at least 20 minutes, or five or more days of moderate-intensity activity or walking for at least 30 minutes or $\geq$ 5 days of any combinations of walking, moderate, and vigorous activity.

3. Results

3.1. The Prevalence of Leisure-Time Physical Activity/Inactivity

3.1.1. Adults

Low physical activity as the health levels in our society are increasingly dangerously. According to the TLGS study, during 2000 - 2004 (phase II of TLGS), the prevalence of leisure-time low physical activity was 69.8% and the prevalence of physical activity was 30% for both genders, among total TLGS population (n = 72850). The levels of leisure-time physical activity of 1590 men (50.6%) and 1803 women (43.5%) were less than 30 min/week. As expected, the prevalence of inactivity increased as BMI increased (69.8% in overweight men and 75.3% in obese men; P < 0.05). In addition, low physical activity level in occasional smokers was 36% higher than in never smokers (P = 0.002) (10). Another study in TLGS participants with no history of lifestyle intervention during the phase II (3515 TLGS adults), showed a significant decrease in leisure-time physical activity among women (P < 0.05), after a 6.5-year follow up. The prevalence of low physical activity in this study decreased significantly between phases II and IV of TLGS, (45.9% vs. 42.6%, P < 0.05), especially among older men ($\geq$ 60 year). Eventually, results indicated a 3.3% decrease in the prevalence of low physical activity during a 6.5 year follow up (11). Although a decrease in low physical activity has been observed, it's prevalence still remains high.

3.1.2. Adolescents

Physical activity undoubtedly is related to the obesity status of adolescents (12). Published TLGS data reveal that, among 777 adolescents participants, 50.4% of individuals with normal weight and 44% of overweight/obese adolescents (BMI $\geq$ 85th percentile) had high levels of physical activity ($\geq$ 6 MET of intensity), levels which were 0.8 $\pm$ 0.4 and 0.6 $\pm$ 0.2 h/day in the normal weight and overweight/obese groups, respectively, indicating that most of the TLGS adolescents have moderate and high physical activity (13).

3.2. Physical Activity and Metabolic Syndrome

The physical activity and the components of metabolic syndrome (MetS), i.e. waist circumference (WC), fasting blood glucose (FBG), Triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), systolic blood pressure (SBP), diastolic blood pressure (DBP), have been investigated in the TLGS population and have been known to be associated with each other; means of mentioned variables were significantly higher in the overweight/obese adolescents, except for HDL-C and FBG in each tertile of physical activity. In normal weight individuals, there was a significant association between light physical activity and the risk of lower levels of HDL-C (P: 0.01). Overweight/obese subjects with light and moderate physical activity levels had larger WC than those who participated in vigorous physical activity, only after adjustment for determined confounders (OR = 1.11; CI 95% 1.07, 1.21; P: 0.01) (OR = 1.06; CI 95% 1.01, 1.08; 0.02, respectively) (13). Data from 5568 (2486 male, 3082 female) non-diabetic participants aged $\geq$ 20 years in TLGS (phase IV, 2008 - 2010) shows that in both genders, the most pre-diabetic patients were not active in leisure-time physical activity, compared to non-prediabetic controls (P < 0.01). Prediabetic male participants had indirect association with both poor diet and physical activity, via BMI and TG, respectively, prediabetic female participants. Whereas these association has been between behavioral factors and pre-diabetes were via TG, respectively in prediab. Leisure-time physical activity and poor diet were significantly correlated, only in men (P <

0.01) (14). Higher risk of MetS was detected in Overweight people with a sedentary lifestyle compared to who had high leisure-time physical activity levels in phase IV of TLGS (15). In brief, results of these studies showed the impact of physical activity on MetS components and some MetS component review as below:

3.2.1. Hypertension

In the obese group, SBP differed significantly by leisure-time physical activity categories (106.9 ± 14.3 mmHg vs. 119.1 ± 17.2 mmHg, P = 0.03). Normal-weight participants with high leisure-time physical activity had a greater risk of high SBP than did those who had leisure-time physical activity moderately (OR, 0.52; 95% CI, 0.31 - 0.86; P = 0.01), the similar risk was detected in obese people whit vigorous leisure-time physical activity, compared to those who had light leisure-time physical activity (OR, 0.60; 95% CI, 0.41 - 0.91; P = 0.01) and moderate leisure-time physical activity (OR: 0.58; 95% CI, 0.39 - 0.64; P = 0.005) (15).

3.2.2. Dyslipidemia

In the obese group, TGs levels differed significantly by leisure-time physical activity categories (111.4 ± 1.6 mg/dL vs. 147.1 ± 1.6 mg/dL, P = 0.01). (15). Normal-weight adults who participated in light leisure-time physical activity had a higher risk of elevated triglycerides and reduced HDL-C, than did adults who participated in vigorous leisure-time physical activity (OR, 1.46; 95%; CI, 1.01 - 2.14; P = 0.049) (OR, 1.15; 95% CI, 1.05 - 2.33; P = 0.03); hence the results demonstrated that for the normal-weight group with a sedentary lifestyle, the risk of having higher triglyceride levels was 46% and in those with lower HDL-C was 15% higher than for those with vigorous leisure-time physical activity (15).

3.2.3. Dysglycemia

In the overweight group, adults who participated in moderate leisure-time physical activity had higher FBG levels than those with vigorous leisure-time physical activity after adjustment for sex, age, smoking status, education levels, and calorie intake (OR, 1.65; 95% CI, 1.37 - 3.23; P = 0.02); the association between MetS and light leisure-time physical activity was significant only after adjustment for those variables (OR, 2.08; 95% CI, 1.03 - 4.21; P = 0.04). Overweight individuals with vigorous leisure-time physical activity had lower FBG than groups with moderate leisure-time physical activity (15).

3.3. Low Physical Activity and Obesity

Logistic regression analyses of 7285 adults in phase II of TLGS, revealed that rates of low physical activity of men with BMI > 30 kg/m^2 were significantly higher than the rates of physical activity of men with BMI < 25 kg/m^2 (P = 0.001). There was no significant difference between the BMI 25 - 30 kg/m^2 group and the reference group in men (10). On the other hand, another study showed no significant difference between BMI groups regarding leisure-time physical activity categories during phase III of TLGS (2005 - 2008) (15). Analysis of different TLGS phases yielded different results on the association between physical activity and obesity.

Mother's physical activity could affected the prevalence of children obesity with mean ages of 5.3 and 9.1 year. Across quartiles of mother's physical activity, from heavy to light, the prevalence of obesity increased among children, from 4.4% to 5.9% in children, aged 5.3 year (P = 0.02) and from 11.6% to 13.0% in children, aged 9.1 year (P = 0.03). The father's physical activity had little effect on the prevalence of children obesity (mean age 5.3 year) (12). hence apparently parent's physical activity and physical activity at any age could have an impact on body weight and obesity.

3.4. Social and Behavioral Factors

Two TLGS study have focused on physical activity as a dependent factor and aimed assessment of the effect of the social and behavioral factors on physical activity. Among 7285 TLGS participants in phase II, there was no statistically significant difference between the prevalence of low physical activity based on age, smoking, educational levels and hours worked; the prevalence of inactivity only increased with age from 20 to 49 in men (P = 0.001) (10). In another survey, the assessment of a conceptual model of associations between socio-demographic, behavioral factors and obesity showed that in both genders, being employed and having lower levels of education significantly lowered leisure-time physical activity in phase IV of TLGS (P < 0.01), and also, men are married had significantly lower leisure-time physical activity (P < 0.01) (16); these results are not sufficient and for these studies on study the association between social and behavioral factors and physical activity are needed.

4. Discussion

The present review indicates the impacts of low physical activity on the health of the community from adolescence to adulthood. The prevalence of low physical activity among adults was 69.8% and a significant increase in physical activity was documented in a 6.5-years follow up. A Brazilian study showed 66.6% low physical activity in adults, data is almost as same as very similar to our results (17). The significant increase in physical activity was also observed from 1999 to 2009 in Switzerland (18). It needs to be mentioned that the questionnaires used were different.

Our results revealed that physical activity is associated with some of the MetS components in both adolescents and adults, results consistent with other studies that revealed moderate and high physical activity is related with lower risk of MetS in adolescents (8) and adults (19). It is obvious that low physical activity during childhood and adolescence could affect adult low physical activity and increase non-communicable disease risk factors such as BMI, high blood pressure in the future (20, 21). Based on our results, physical activity interventions could be an effective strategy and have a positive impact on reducing the components of non-communicable diseases such as BMI, WC, and SBP not only in adolescence, but also in adulthood. Public health efforts must be increased to improve the physical activity levels to prevent the non-communicable diseases and other related diseases.

TLGS studies focusing on physical activity, of course, do have some limitations; first, the prevalence of physical activity was not assessed in children; second, the data are obtained based on self-report questioners and study outcomes may hence have recall bias; third, because of using different physical activity questionnaires and methods from other studies, any generalization of this study to others could be problematic; fourth, there is much physical activity data that has not been released yet, and hence many gaps in data available. Future studies are hence needed to determine the prevalence of all TLGS phases from childhood to adulthood, and to identify clinical aspects of physical activity. Interventions for physical activity, of course must be continued in TLGS population.

4.1. Conclusion

The present review highlights the impact of low physical activity on the health of the TLGS community from adolescence to adulthood. The decreased prevalence of low physical activity from phase II to phase IV of TLGS indicates the necessity for lifestyle interventions as a potentially effective strategy, which could have a positive impact on various risk factors and indicators of non-communicable diseases such as BMI, WC, SBP, and lipid profiles.

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Tobacco Smoking: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: Smoking is a global public health priority and accurate data of the local population is essential to improve the health policies against its use. Hence, this study aimed to summarize the important findings available on the prevalence of smoking and its association with non-communicable diseases, documented by one of the largest prospective community-based studies of Iran.
Evidence Acquisition: All articles derived from the Tehran Lipid and Glucose Study (TLGS) in the last two decades, from the earliest publications until 30 January 2018 were reviewed for their findings on tobacco smoking.
Results: The prevalence of smoking in non-diabetic adults $\geq$ 20 years increased between baseline (phase I, 1999 - 2001) and follow-up (phase V, 2008 - 2011) from 25.5% to 35.4% among men and from 3.4% to 6.8% among women. In TLGS adolescents (10 - 18 years) water pipe use increased between 2003 and 2005 from 35.5% to 40.9% among boys and from 19.7% to 26.1% among girls. Regarding health hazards, smoking in men was associated with increased risk of combined impaired fasting glucose/impaired glucose tolerance [hazard ratio (HR) 1.69; confidence interval (CI) 95% 1.15 - 2.48] and hypertension (HR 1.26; CI 95% 0.98 - 1.63). Moreover, men, even smoking less than 10 cigarettes per day, were at increased risk for cardiovascular diseases by HR 2.12 (CI 95% 1.14 - 3.95). For women, the risk of chronic kidney disease dramatically increased 5.74-fold (CI 95% 2.71 - 12.15) among smokers. In the whole population, smoking contributed to 7.7% of all-cause mortality with HR 1.75 (CI 95% 1.38 - 2.22). Other health aspects of tobacco smoke, including its impact on metabolic status, thyroid function, female reproductive system and life style have also been reviewed.
Conclusion: Considering hazards of smoking, there is the urgency for more effective preventive measures in Iran; emphasizing the need for further local studies on the hazards of smoking with special attention to women and adolescents and the independent hazards of water pipe use.

Keywords: Smoking, Tobacco, Cigarettes, Water Pipe, Prevalence, Risk

1. Context

Tobacco, known as the world's leading killer, is a major preventable disease risk factor (1). Smoking tobacco is responsible for the highest global disease burden, after high blood pressure (2). It can cause various non-communicable diseases (NCDs) including about 25% of ischemic heart events, 70% of chronic obstructive pulmonary diseases, and 90% of lung cancers (3).

In 2008, WHO issued a warning about the fatal tobacco epidemic, and predicted an increase in the annual tobacco-related mortality from 5.4 million at the time, to 8 million by 2030. More than 80% of the global burden of smoking is on low-to-middle income countries, where opposed to high-income countries, the prevalence of smoking is increasing. Unfortunately, these countries have limited resources to take preventive measures against tobacco use and are the main target of the tobacco industry (1). According to the sixth national survey of NCD Risk Factors Surveillance, in 2011, the rate of tobacco smoking in Iran was estimated to be about 10% among adults (19.2% in men and 0.6% in women), which was lower than most countries of the West and Middle East (4). Yet, despite various preventive measures Iran, the trend of smoking among adults has not decreased in the past two decades (5, 6). Moreover, the prevalence of smoking among adolescents seems to be increasing (7). According to the CASPIAN Study, in 2011 - 2012,

5.9% of the Iranian youth (aged 6 - 18 years) had smoked tobacco during their lives, which is higher than most Western and other Middle Eastern countries (4). Hence, a steep rise in the prevalence of smoking is expected in Iran, unless effective measures are implemented to prevent tobacco use. Raising awareness of the hazards of smoking is one of the most important steps of preventive programs (1), for which accurate local data on the risks of smoking is essential.

This review aimed to provide vital information on tobacco use and its risks, based on results from one of the largest cohort studies in Iran. Tehran Lipid and Glucose Study (TLGS) is an ongoing large scale and community-based cohort, initiated in 1999 to help design and implement effective strategies against NCDs and their risk factors in a population of urban families from Tehran. During its years of investigation, the TLGS has documented valuable information about the prevalence, facilitators and hazards of smoking which have been summarized here.

2. Evidence Acquisition

Articles from the TLGS that were published or accepted for publication in a journal prior to 30 January 2018 and included data on tobacco use, were reviewed with the aim of providing a summary of the important findings of TLGS on smoking.

3. Results

3.1. The Prevalence and Secular Trends of Smoking

Data from the first phase of TLGS (1999 - 2001) revealed that among individuals aged $\geq$ 15 years, 12% were smokers at the time (10.6% daily smokers, 1.5% occasional smokers) and 6.1% were past smokers. The prevalence of smoking among women was as low as 2% compared to 22% among men which increased with aging in both genders, reaching a maximum of 4.3% among women and 38.1% among men at ages 35 to 44 years (8). Among the elderly (aged > 60 years), we found a relatively lower rate of 17% in men and 2% in women, equal to an overall 10% among both genders. About 15% of the elderly population were past-smokers (9).

After a decade of follow-up, separate analyses for diabetic and non-diabetic adults revealed increase in smoking prevalence among TLGS women, from 3.17% to 4.95% for diabetics and from 3.39% to 6.82% for non-diabetics (10). The prevalence of smoking also increased among non-diabetic TLGS men, from 25.5% to 35.4% over a period of 10 years. For diabetic men, the rates increased from 20.18% to 24.23%, but not significantly (P value = 0.107) (Figure 1) (10). Among the elderly, smoking trends remained steady after a decade (11). Regarding adolescents, a TLGS school survey in 2003 showed that 35.5% of boys and 19.7% of girls were current water pipe smokers according to the definition of Global Youth Tobacco Survey (GYTS), i.e. had smoked water pipe in the previous 30 days. The corresponding rates increased significantly after two years to 40.9% and 26.1%, respectively (12).

Noting the unfavorable trends of smoking among the youth, the main facilitators of smoking were assessed among young men of TLGS, classifying the main effective factors into two categories including the personal motivators: (1) fulfilling essential needs, (2) search for identity, (3) lack of life skills, and the environmental factors: (1) social patterns (i.e. being impressed by smoker parents and peers), (2) ease of access (13).

3.2. Smoking and Non-Communicable Diseases

The findings of TLGS on the association of smoking with non-communicable diseases are summarized in this section. Moreover, details on studies with major clinical outcomes have been presented in Table 1.

3.2.1. Pre-Hypertension and Hypertension

Findings from the TLGS have shown that after a decade long follow-up, neither current nor past smoking was associated with increased risk of pre-hypertension (20). Furthermore, smoking was not associated with isolated systolic or diastolic hypertension after adjusting for other common risk factors (21). However, in an attempt to develop a point-score system to predict incident hypertension in nondiabetic individuals, Bozorgmanesh et al. indicated that smoking was independently associated with hypertension among men, to a marginally significant level (HR: 1.26; CI 95%: 0.98 - 1.63), but they failed to find any associations for active or passive smoking among women (14).

3.2.2. Pre-Diabetes and Type 2 Diabetes

Regarding pre-diabetes phenotypes, after the important risk factors of family history of type 2 diabetes and fasting plasma glucose, current smoking had the highest hazard ratio (HR) for developing combined impaired fasting glucose/impaired glucose tolerance among men (HR: 1.69; CI 95%: 1.15 - 2.48) (22). However, current smokers were not at increased risk for incident type 2 diabetes, neither among women nor among men, after almost a decade (15). More specifically, neither current, nor past smoking were associated with insulin resistance or β-cell dysfunction, as calculated by the HOMA-IR and HOMA-b formulas, respectively (23). Additionally, among TLGS adolescents, passive smoking was not associated with early adulthood pre-diabetes/type 2 diabetes (24).

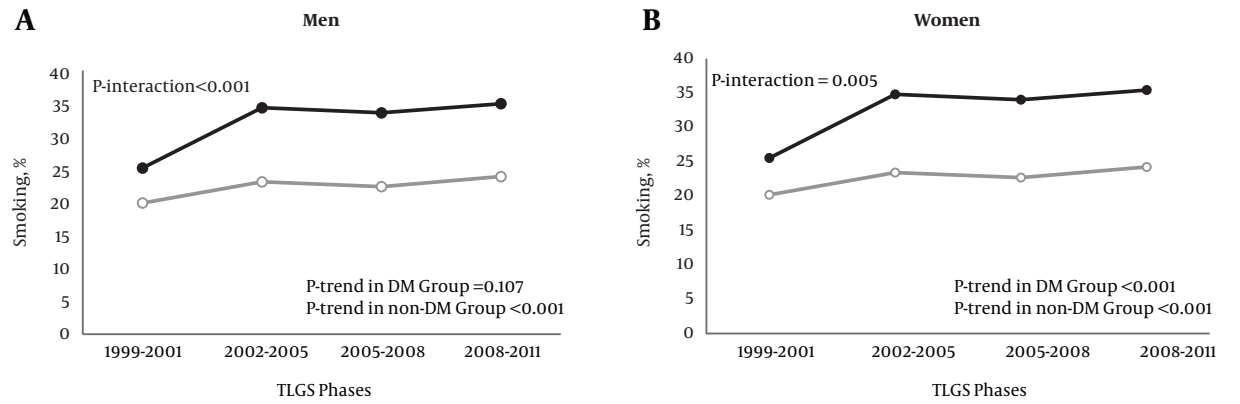

Figure 1. Age-adjusted prevalence of smoking among diabetic and non-diabetic men and women in phases I-IV of the TLGS. Age-adjusted prevalences of smoking for diabetic and non-diabetic men (A) and women (B) were derived from data presented by Jahangiri-Noudeh et al. (10). White circle = diabetic group; black circle = non-diabetic group; DM, diabetes mellitus; phase I (1999 - 2001), phase II (2002 - 2005), phase III (2005 - 2008), phase IV (2008 - 2012); TLGS, Tehran Lipid and Glucose Study.

Table 1. Associations Between Smoking and Major Clinical Outcomes in the Tehran Lipid and Glucose Study[a]

Study	Follow-Up, y	Sex (N)	Smoking Definition	Outcome	Confounder Adjustments	HR or OR (CI 95%)
Bozorgmanesh et al. (14)	6	M (2695)	Current smoker (reference: Past/never smoker)	Hypertension	Age, SBP, DBP, FHCVD, WC, age by SBP	HR (M): 1.26 (0.98 - 1.63)
Derakhshan et al. (15)	9.5	M (3620), F (4780)	Current smoker (reference: Past/never smoker)	Type 2 diabetes	None	HR (M): 0.97 (0.75 - 1.26), HR (F): 0.96 (0.53 - 1.76)
Tohidi et al. (16)	9.9	M (1454), F (1859)	Current smoker (reference: Never smoker)	Chronic kidney disease	Age, eGFR, diabetes status, marital status, HCVD, education, hypertension, dyslipidemia, abdominal obesity, BMI, FHCVD	OR (M): Not applicable*, OR (F): 5.74 (2.71 - 12.15)
Khalili et al. (17)	10.3	M (2889), F (3803)	Current smoker (reference: Past/never smoker)	Coronary heart disease	Age, FHCVD, hypertension, diabetes, total-cholesterol, HDL-c	HR (M): 1.60 (1.20 - 2.0), HR (F): 1.20 (0.6 - 2.4)
Parizadeh et al. (18)	12	M + F (3088)	Current smoker (reference: Past/never smoker)	Ischemic stroke	Age, sex, wrist circumference, WC, DBP, FPG, eGFR, FHCVD	HR: 1.96 (1.13 - 3.42)
Sardarinia et al. (19)	10.7	M + F (7635)	Current smoker (reference: Past/never smoker)	Cardiovascular events	Age, sex, BMI, education, FHCVD	HR: 1.53 (1.27 - 1.83)
Sardarinia et al. (19)	10.7	M + F (7635)	Current smoker (reference: Past/never smoker)	All-cause mortality	Age, sex, BMI, education, FHCVD, HCVD	HR:1.63 (1.29 - 2.06)

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FHCVD, family history of cardiovascular disease; FPG, fasting plasma glucose; HCVD, history of cardiovascular disease; HDL-c, high density lipoprotein cholesterol; HR, hazard ratio; OR, odds ratio; SBP; systolic blood pressure; WC, waist circumference.
[a]Multivariate analysis not performed due to nonsignificant association in the univariate model.

3.2.3. Chronic Kidney Disease

Among the TLGS population, smoking was an independent risk factor for stages 3 - 5 of chronic kidney disease (CKD) in women which dramatically increased the risk about 6-fold for current smokers (HR: 5.74; CI 95%: 2.71 - 12.15), but no longer remained significant among past smokers (HR: 1.67; CI 95%: 0.66 - 4.22). However, no associations were found among men (16).

3.2.4. Metabolic Syndrome and Metabolic Risk Factors

Regarding metabolic syndrome, smoking was not associated with increased risk among TLGS women or men (25); however, it has been shown to adversely affect the physical quality of life among TLGS men (26) In another TLGS investigation, Ramezankhani et al. applied the self-organizing map algorithm to cluster five metabolic risk factors (high body mass index (BMI), high systolic blood pressure, low glomerular filtration rate, high total-cholesterol and high fasting plasma glucose) and assess the corresponding risks of incident CVD. Surprisingly, smoking was significantly more prevalent among men in the healthier clusters and women who had quit smoking were assigned to the higher risk clusters. These findings may reflect the favorable effects of smoking on some metabolic risk factors, such as BMI or blood pressure (27); However, this does not overshadow the hazardous cardiovascular effects of smoking which are discussed as follows.

3.2.5. Cardiovascular Diseases

Smoking has been one of the conspicuous modifiable risk factors of CVD in the TLGS population. Almost 7.6% of all CVD events were attributed to current smoking, increasing CVD risk by 61% (19). In a detailed investigation among men, after adjustment for duration of smoking in addition to common CVD risk factors, current smoking showed an even stronger association with a hazard ratio of 2.12 (CI 95%: 1.14 - 3.95) for smoking less than 10 cigarettes per day and 6.05 (CI 95%: 2.83 - 12.92) for more than 20 cigarettes per day. The higher risk of CVD persisted after smoking cessation (HR: 2.42; CI 95%: 1.28 - 4.56) (28). Current smoking also increased the risk of premature CVD among men (HR: 1.68; CI 95%: 1.12 - 2.51) and was responsible for almost 20% of the events; however, the risk was nonsignificant among past smokers (29). Regarding coronary heart disease (CHD), after 10 years of follow-up, smoking (current or past) was the second most prevalent modifiable risk factor of CHD among men (HR: 1.6; CI 95%: 1.2 - 2.0) with an average population attributable fraction (PAF) of 7%; however, no significant risk was detected among women (17). In the detailed analysis among men, after adjustment for duration of smoking besides other risk factors, the HR ranged from 1.89 (CI 95%: 0.96 - 3.7) for less than 10 cigarettes per day to 4.12 (CI 95%: 1.75 - 9.71) for over 20 cigarettes per day among current smokers and the risk persisted among past smokers (HR: 1.64; CI 95%: 0.81 - 3.35) (28). In another study with an extended follow-up of 12 years, past-smoking per se was associated with 83% increased risk of CHD (CI 95%:1.30 - 2.59) (30). Of-course, regarding past smokers, the risk may disappear given more time. Also, in a comparison of smoking-related risk between diabetic and nondiabetic men, we demonstrated that diabetes did not alter the smoking-induced risk for CHD/CVD. Moreover, after twelve years of follow-up, smoking habits of nondiabetic men independently increased the risk for CHD and CVD by 49% and 53%, respectively (P values < 0.001) (31). Regarding cerebrovascular events, the association between smoking and ischemic stroke was marginally significant after 9 years (HR: 1.73; CI 95%: 0.97 - 3.08; PAF 14.5%) (32), but grew stronger after 12 years of follow-up (HR: 1.96; CI 95%: 1.13 - 3.42) (18). Lastly, in a cross-sectional investigation of cardiovascular risk factors in adolescents, smoking was associated with increased levels of total cholesterol ($\beta = 0.11$, P value = 0.012) and LDL ($\beta = 0.4$, P value = 0.001) among TLGS boys (33).

3.3. Smoking and Mortality

Results on all-cause mortality after over a decade long follow-up, indicated a hazard ratio of 1.75 (CI 95%: 1.38 - 2.22) and a PAF of 7.71% (CI 95%: 3.85 - 11.54) for current smoking (19). An investigation launched on the TLGS type 2 diabetics pointed out that smoking (past/current) was associated with mortality among these patients with HR 1.45 (CI 95%: 1.45 - 1.03) and PAF 11% (34); However, an extended follow-up revealed that its association with mortality did not differ significantly between diabetic and non-diabetic men (P value > 0.46) (31). In another study, further analysis among men showed that the risk of mortality was attributed to the amount of daily cigarette smoking, independent of its duration. Regarding all-cause mortality, the association was only significant when smoking over 10 cigarettes per day, showing about four times higher risk, compared to non-smokers (P value < 0.001); whereas, the hazard ratio of CVD-mortality ranged from 4.57 (CI 95%: 1.32 - 15.79) for smoking less than 10 cigarettes/day and dramatically increased to 12.06 (CI 95%: 3.19 - 45.46) for more than 20 cigarettes/day. The association between smoking and mortality did not persist among past smokers (28).

3.4. Smoking and the Female Reproductive System

Smoking has been known to have anti-estrogenic effects on women (35). Among TLGS women, active smoking was associated with earlier menopause (P value = 0.05) (36) whereas passive smoking during childhood did not alter age of menarche (37). Regarding pathologies of the reproductive system, a cross-sectional analysis revealed that despite its relatively low prevalence, smoking was related to primary infertility in women (OR: 1.47; CI 95%: 1.38 - 3.53) (38). For abnormal uterine bleeding, the increased hazard among smokers was not significant after multivariable adjustment (P value = 0.65) (39).

3.5. Smoking and Thyroid Function

According to a cross-sectional observation of the euthyroid population of TLGS, after adjustment for age and BMI, the mean value of Ln TSH was significantly lower in current/past smokers, compared to non-smokers (0.36 ± 0.82 vs. 0.6 ± 0.82; P value < 0.001) and the frequency of positive thyroperoxidase antibody was lower among current/past smokers compared to non-smokers (6.7% vs. 13.5%; P value < 0.001). Moreover, the prevalence of hypothyroidism (TSH > 5.8 mU/L) was significantly lower among current/past smokers vs. non-smokers (OR 0.4; CI 95% 0.2 - 0.8), but the prevalence of hyperthyroidism (TSH < 0.3 mU/L) did not differ significantly between the two groups (P value = 0.28) (40). However, a recent longitudinal investigation on the natural course of euthyroidism among TLGS subjects revealed that after 6 years of follow-up, smoking was only associated with progression to overt hyperthyroidism (TSH < 0.34 mU/L and serum free T4 > 1.55 ng/dL) (41).

3.6. Smoking and Life Style

Smokers among the TLGS population generally had a less healthy life style. As Asghari et al. demonstrated, smoking was more frequent among Tehranian adults with lower quality diets, judged by the Healthy eating index-2005 score (42). Moreover, cigarette smoking was associated with lower physical activity during leisure time among TLGS men (43).

3.7. Smoking Water Pipe

Although some of the TLGS articles have reported the hazards of water pipe use pooled with cigarette smoking, the risk caused independently by water pipe is still understudied. In one investigation, Ghasemi et al. assessed the effect of cigarette and water pipe smoking on the level of nitric oxide (NO) metabolites in serum and showed that both water pipe and cigarette smoking were associated with NO overproduction, which may be associated with further CVD risk (44).

3.8. Response to Preventive Measures

The first phase of the TLGS was a cross-sectional survey to investigate NCD and its risk factors. Following baseline data collection on phase I, lifestyle interventions were employed on a subgroup of individuals in follow-up phase II, with the aim to promote health. Smoking cessation was one of the three main arms of behavioral interventions, along with modifying nutrition and physical activity. Participants were educated and supported to stop smoking by a consultant through in-person consultations and relevant brochures, in a quit smoking clinic (45). After about 3.6 years, smoking cessation rate was 70% higher in the intervention group compared to the control group (P value = 0.01) (46).

4. Discussion

This study summarizes the key findings of the TLGS on the prevalence, facilitators and long-term hazards of smoking tobacco in a community representing the general population of Tehran. Overall, we highlighted the role of tobacco smoking as a major risk factor for CVD, CHD, ischemic stroke, CKD, hypertension and mortality in an Iranian population. Smoking also affected thyroid function tests and the female reproductive system.

Despite the TLGS life style interventions aimed at smoking prevention, the overall prevalence of smoking has not decreased in the last two decades. More importantly, the increasing trends of smoking among women and the high and rising prevalence of water pipe use among adolescents, are alarming signs for higher smoking rates in the future. In general, in line with national surveys (5, 6), smoking rates at baseline were lower among TLGS women compared to western countries as estimated in the recent global reports of WHO (4), which could be attributed to the less social acceptability of smoking for women in Iran. However, a rise of female smokers was noticed in the previous decade which was higher in the TLGS compared to a simultaneous national systematic review that included reports from several cities of Iran, besides Tehran (6). The difference between surveys is not surprising, since there are generally less social limits on women in Tehran compared to other cities of Iran. Regarding adolescents, the prevalence of using tobacco products other than cigarettes (mostly in the form of water pipes) in the GYTS report of 1999 - 2001 was considerably lower in European and other Middle Eastern regions (all rates below 15%), compared to the TLGS (47). This may be attributed to the traditional aspect of water pipe use in Iran which has made it more socially acceptable (48). Overall, these findings indicate that preventive programs against smoking need to be upgraded in Iran. According to the WHO report on the national tobacco control program, evaluated by the MPOWER measures, Iran has performed well in many aspects of smoking control including smoke-free policies, smoking cessation programs, health warnings on cigarette packages, anti-tobacco campaigns and bans on advertising for tobacco use. However, taxation, which is considered the most effective way to discourage smoking, has been overlooked in our country (49).

The strengths of this study are that it summarizes the findings of community-based investigations with long-term follow-ups, derived from one of the largest cohort

studies in the Middle East and the results are not derived from a specific population (e.g. students), unlike many other local studies on smoking (6). In addition, all of the included studies have used a unified definition for smoking habits according to the WHO guidelines (50). There are also some limitations. Firstly, due to the low prevalence of smoking, many of the studies could not report on the hazards of smoking among women. Secondly, although in many studies smoking was attributed to all forms of smoked tobacco including water pipe, data on the independent hazards of water pipes are lacking, which is particularly important due to the popularity this form of tobacco use in Iran (48). In addition, data on smoking status were based on self-reports and no paraclinical assessments, such as serum cotinine levels, had been obtained, which may lead to underestimation of smoking rates, since there is a negative attitude in our culture towards smoking, especially for women. In this regard, comparing results of serum cotinine levels with the corresponding self-reports, Sarraf-Zadegan et al. reported a significant rise in rates of tobacco use(10.6% rise among men and 14.6% rise among women) (51). However, to reduce the bias, interviews in the TLGS were performed in a private setting and women have been questioned by female interviewers. Moreover, since most studies have considered smoking as a binary variable, they lack information on the duration and intensity of smoking or the time passed from smoking cessation. Lastly, although most studies made adjustments for a wideset of variables, further adjustments could alter the associations, e.g. life style interventions and nutrition could affect NO levels in serum in the study by Ghasemi et al. (44).

4.1. Conclusion

Considering the various health hazards which have been summarized in the current study, smoking should remain a priority in public health policies. In order to improve preventive measures, future studies are required to determine the impact of population-based interventions against smoking. In addition, more attention must be focused on smoking among women and adolescents and the hazards of other types of tobacco use, such as water pipe.

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Biochemical Assessment: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: The Tehran Lipid and Glucose Study (TLGS) is a community-based study to reveal the frequency of non-communicable diseases (NCDs) in Tehran's population. This research consists of two main parts, a cross-sectional study on the prevalence of cardiovascular risk factors and a 20-year-ongoing prospective cohort study, which was initiated in 1999 in several phases with an approximate duration of 3.6 years, and is still ongoing. The aim of the present study is review the 20 year biochemical findings of the TLGS related to the NCDs in a large sample.

Methods: All articles on biochemical assessments derived from the TLGS from the earliest publications (2002) until 30 January 2018 were reviewed for their findings on different risk factors of NCDs.

Results: According to the TLGS findings high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), homocysteine (Hcy), age, smoking, hypertension, and obesity were the most important risk factors of cardiovascular diseases (CVD). It was illustrated that in subjects with abdominal obesity, the hs-CRP and IL-6 serum levels were higher than in normal subjects. The most appropriate prognostic indexes and associations were for hs-CRP, IL-6, and Hcy with abdominal obesity, waist circumference, WHtR, and wrist circumference, respectively. Previous studies have demonstrated a direct relationship between obesity and serum levels of inflammatory factors.

Conclusions: According to the results of TLGS, serum levels of biochemical risk factors such as hs-CRP, IL-6, and Hcy could be beneficial in early diagnosis and effective treatment of cardiovascular, obesity and other metabolic diseases.

Keywords: TLGS, Iran, Biochemistry, Inflammatory Factors, Obesity, Metabolic Syndrome

1. Context

The highest prevalence and incidence of non-communicable disease (NCD) is related to cardiovascular, diabetes, obesity, and metabolic syndrome (MetS). MetS is a common clinical disorder characterized by the presence of three or more of five feature i.e. obesity, hyperglycemia, hypertension, low high density lipoprotein-cholesterol (HDL-C), and hypertriglyceridemia (1). MetS is a risk factor for cardiovascular disease (CVD), type 2 diabetes (T2D), and cancer. The main role of inflammation in the growth and progression of atherosclerosis has been documented, important roles are attributed to inflammatory cytokines such as interleukin-6 (IL-6) and high sensitivity C-reactive protein (hs-CRP) (2). Recently, in addition to a prognostic factor for the development and progression of CVD, homocysteine (Hcy) has been proposed as a risk factor. Hcy levels increase to 30% in patients with atherosclerosis and only 12% elevation than normal is related with a 3-fold rise in the risk of myocardial infarction (3, 4). Obesity is a public health problem worldwide in both poor and rich communities, and is associated with NCDs. Adipose tissue stores surplus triglycerols and acts as an endocrine organ by releasing adipokines that play roles in regulating appetite, insulin resistance, glucose and lipid metabolism, and inflammation; chronic inflammation or excessive response can lead to harmful effects (5).

TLGS is based on community being conducted to investigate the prevalence of NCDs and to provide population-based criteria aimed at reducing the prevalence or prevention of a growing risk factors for NCD. This research consists of two main parts, a cross-sectional study on the prevalence of cardiovascular risk factors and a 20-year-old prospective cohort study, conducted in several phases at intervals of duration of 3.6 years from 1999, and is still

ongoing. Participants included 15005 citizens, > 3 years, from district 13 of Tehran classified by cluster sampling. This area based on population distribution it represents the general population of Tehran (6).

Among various related risk factors assessed this study only reviewed data on the biochemical risk factors of NCD. Although risk factors such as lipid components (triglycerides, HDL-C, LDL-C, total cholesterol), glucose, insulin, thyroid stimulating hormone, and thyroxine can be considered as biochemical or molecular risk factors, but focus of this article is on CRP, IL-6 and Hcy and their associations with anthropometric parameters. Visfatin as a product of visceral adipose tissue, considered as a helpful Insulin mimic hormone, and its associations with the mentioned risk factors has also been reported.

2. Methods

All articles contain biochemical, or IL-6 or Hcy or CRP and TLGS in their title in PubMed, SID, ScienceDirect, and Medline from the earliest publications (2002) until 30 January 2018 were reviewed for their findings on different risk factors of NCDs.

3. Results

3.1. Biochemical Risk Factors

3.1.1. C-Reactive Protein (CRP)

CRP is an acute phase reactant and an inflammatory marker (7). Acute phase reactants are created in hepatocytes and their production is regulated by cytokines such as TNF-α and IL-6; CRP, which is known as a sensitive and classical acute phase reactant, is a highly susceptible inflammatory systemic marker, and its serum levels rapidly rises in response to various motivations (8). CRP increase is associated with cardiovascular risk. Vessel inflammation or maybe the renin-angiotensin system plays an important role in hypertension, and CRP concentrations are significantly higher in subjects with hypertension (9). It has been shown that CRP levels increase in patients with high body mass index (BMI). The largest data set available on obesity related to CRP is the Third National Health and Nutrition Examination Survey of the US population conducted between 1988 and 1994. Obesity increased an odds ratio (OR) for having greater CRP (2.13 for men and 6.21 for women) after adjusting for other variables (10). Anthropometric measurements including height, weight, hip circumference, waist circumference (WC), wrist circumference, waist to hip ratio (WHR), and waist to height ratio (WHtR) were recorded in each phase of the study. Abdominal obesity was defined by cutoff WC $\geq$ 91 cm for women and $\geq$ 89 cm for men.

Hosseinzadeh-Attar et al. on a subsample of TLGS project in a well matched case control study (37 MetS and 37 matched controls, 46.35 $\pm$ 1.6 years), determined associations of anthropometric, biochemical profiles, and CRP with Visfatin. No significant association between CRP and Visfatin serum level found, but a significant correlation between CRP with BMI, WC and WHR was found. Visfatin level was significantly lower in patients with MetS (11). Zarkesh et al. on 365 individuals (160 MetS and 205 matched controls) revealed that the levels of hs-CRP were higher in MetS subjects; an interesting finding was a slow and significant rise in the hs-CRP levels in association with increasing numbers of MetS components. The best predictors for the level of hs-CRP in the MetS subjects were hip, WHtR, and height (12, 13). Associations between inflammatory factors and obesity in TLGS, in a cross sectional study (132 Men and 222 women, 46.1 $\pm$ 16.1 years) were assessed by Faam et al, and obtained data showed a higher level of hs-CRP in the abdominally obese group (14, 15).

In TLGS, 80 diabetic individuals were selected randomly, and compared with 73 participants who did not have diabetes in two phases as controls. Who had diabetes during the study were more obese (central and general) and had higher fasting and two hours' glucose and insulin resistance, compared to the control group, their serum levels of fasting insulin, CRP, triglycerides, systolic and diastolic blood pressure (SBP and DBP), total cholesterol (TC) ratio to HDL-C was higher and HDL-C levels were lower. In addition, family history of diabetes was more common in them. The highest correlation was found between CRP and BMI (r = 0.51, P < 0.01) and WC (r = 0.45, P < 0.01). CRP was also associated with systolic and diastolic blood pressure, fasting blood sugar (FBS), HOMA-IR, fasting insulin, total cholesterol and triglycerides, but had no significant correlation with HDL-C and 2-hours blood glucose levels. CRP values were equally divided into three parts of the total population. Conditional logistic regression analysis showed that type 2 diabetes mellitus, CRP was predicted by an adjusted model with age (OR = 3.6; CI 95%: 1.5 - 8.2, P = 0.02). The OR of diabetes (model-2), after adjusting with age, systolic blood pressure (SBP), triglycerides, HDL-C was (OR = 2.5; CI 95%: 1.08 - 6.15, P = 0.03). In model 3, after adjusting for age, SBP, triglycerides, HDL-C, HOMA-IR, the OR significantly decreased to 0.8 (CI 95%: 0.2 - 2.8, P = 0.7) (16).

Studies on the relation of CRP and CVD are inadequate to white populations of North America and Europe indicating the need for data on the clinical worth of CRP amount must be confirmed in populations of different ethnic groups and ages. For this purpose, a nested case-control study was conducted on participants of TLGS (126 cases with CVD, 259 control, > 35 years). The cumulative incidence of cardiovascular disease was 1.96% in the studied population and the risk profile of cardiovascular dis-

ease (other than BMI) was more adverse than controls. The median levels of CRP were 1.74 mg/L (inter-quartile range (IQR): 0.76 - 3.19 mg/L) for cases and 0.94 mg/L (IQR: 0.52 - 2.25 mg/L) for controls ($P < 0.001$). Low correlations were detected between CRP and BMI ($r = 0.34$, $P < 0.01$), WHR ($r = 0.22$, $P < 0.01$), Framingham risk score (FRS) ($r = 0.27$, $P < 0.01$). Multivariate logistic regression analysis to obtain the OR of CVD associated with highest quadrant of CRP compared with its lowest quadrant was used in four models. In model one, CRP was the only variable entered, OR of CVD for individuals in the highest CRP quadrant in comparison with the lowest quadrant was (OR = 2.6; CI 95%: 1.4 - 5.1). In the second model, adjustment for the CVD family history, smoking and WHR was not significantly different (OR = 2.3; CI 95%: 1.1 - 4.6, P for trend = 0.02). However, further adjustment with cardiovascular risk factors led to a significant reduction of risk estimate in the third model, (OR = 0.8; CI 95%: 0.3 - 1.9, P for trend = 0.2) or FRS in the fourth model (OR = 1.4; CI 95%: 0.7 - 2.9, P for trend = 0.2). To examine whether CRP increases the predictive value of previous models based on the risk factors of a typical CVD or FRS, the area under the ROC curve (AUC) was calculated and compared for the probability of different logistic regression models with and without the inclusion of CRP. Since, the AUC of a model is its ability to correctly identify cases with and without CVD, it was shown that addition amount of CRP to a model containing conventional CVD risk factors, which in a clinical work, could be easily documented with medical history, physical activity and lipid profile measurement hardly changes the AUC (ΔAUC = 0.006, P = 0.2). The introduction of CRP into another model based on FRS did not significantly change the AUC of the model (ΔAUC = 0.013, P = 0.2). Results indicated that a model based on common risk factors had a better mixture of sensitivity (44%), specificity (92.8%), PPV (76.5%), and NPV (75.6%) than the same model after inclusion of CRP 41.8, 92, 74.2 and 74.3%. In the FRS-included model, adding CRP level slightly improved specificity and PPV, but reduced sensitivity and NPV.

3.1.2. Interluekin-6

IL-6 is a cytokine that have an important role in acute phase reactions, hematopoiesis, bone metabolism, inflammation, energy homeostasis regulation, cancer progression, activity of lipoprotein lipase inhibition, and appetite control/energy absorption at the hypothalamic level. IL-6 is independently associated with cardiovascular risk factors such as hypertension, BMI, and reduction of HDL-C (17, 18). In smokers, the risk of cardiovascular disease is higher. Smoking appears to increase IL-6 production which stimulates CRP production. Trials, including European Concerted Action on Thrombosis and Disabilities study (ECAT), have described an increase in CRP levels in smokers. The Multiple Risk Factor Interventional Trial (MRIFT) study in middle-aged men without CVD indicated that CRP elevation was associated with an increase in CVD mortality (19). In a well matched case control studies (37 MetS and 37 matched controls) by Hosseinzadeh-Attar et al. on a subsample of TLGS project, association of anthropometric, biochemical profiles, and IL-6 with Visfatin were studied. A significantly correlations between IL-6 with BMI, WC, and WHR were found, and no significant association between IL-6 and Visfatin serum level (11). Zarkesh et al. in a subsample of the TLGS, in a cross-sectional study, 365 individuals (160 MetS and 205 matched controls, 46.1 ± 16.1 years), found that levels of IL-6 in MetS subjects was higher, and a significant and gradual increase in the level of IL-6 in association with increasing numbers of components in the MetS group. A strong linear augmentation was observed in the IL-6 levels as the numbers of MetS components increased. In addition, good predictors for the level of IL-6 in the MetS subjects were hip, WHtR and height (12). A higher level of IL-6 in the abdominally obese group were reported by Faam et al. in an association study between inflammatory factors and obesity in TLGS, in the cross sectional study (132 Men and 222 women) (14).

3.1.3. Homocysteine

Hcy is a thiol-containing intermediate metabolite; which in population studies over the past two decades provide evidences on, to direct and independent linkage of that in plasma with the morbidity and mortality from atherosclerosis. Possible mechanisms that link Hcy to atherogenesis include prothrombotic and proinflammatory effects, increased oxidative stress, endothelial dysfunction and smooth muscle cell proliferation. With clinical observations after the initial studies, this factor was included in the list of cardiovascular risk factors (20). Since obesity is considered as a low-grade inflammatory disease, in a cross sectional study, Faam et al. examined the association between Hcy (an inflammatory marker) with obesity-related factors such as BMI, waist, hip in 352 adult TLGS participants (220 women and 132 men, aged $\geq$ 19) randomly enrolled from the population. Linear regression analysis was applied to examine the association between Hcy, anthropometric and biochemical factors. Abdominal obesity was observed in 199 (56.5%) individuals and the level of Hcy was higher in the abdominally obese, the wrist was predictor for Hcy in obese and hip and WHtR were the best predictors for Hcy in the normal group (14). In a similar cross-sectional study, Zarkesh et al. on MetS subjects with a matched control group in a subsample of the TLGS (160 MetS and 206 controls), aged > 19 years (mean of 46.1 ± 16.1 years), the levels of Hcy was higher in subjects with MetS. The best predictor for Hcy level in subjects with MetS was WHtR (12).

3.2. Summary findings of Biochemical factors in TLGS

Previous studies in non-Iranian populations showed that the prevalence of obesity and its co-morbidities is increasing. To evaluate the level of inflammatory markers in subjects with and without abdominal obesity in Iranians, a cross-sectional study was designed on the basis of the TLGS. Of the 352 participants with an average age of 46.1 ± 16.1 years, 199 (56.5%) had abdominal obesity; in this group compared to those without abdominal study, mean of variables of obesity, lipid patterns and inflammatory factors, other than FBS and Hcy were higher. Based on Pearson correlation coefficient, there was a significant correlation between Hcy and height and wrist circumference in the group with abdominal obesity. The positive relationship of hs-CRP with BMI, waist circumference, hip circumference, WHtR, FBS and IL-6 and its negative correlation with height and wrist circumference were statistically significant. A positive correlation was shown between serum levels of IL-6 and WHtR and hs-CRP and a negative correlation was observed with height. In the normal group, a positive correlation was indicated between serum hs-CRP levels and age, BMI, WC, hip circumference, WHR, WHtR, SBP and DBP. Hcy and hs-CRP levels were negatively associated with hip circumference and height, respectively. Using the linear regression analysis, the most suitable predictive indexes for Hcy, hs-CRP, and IL-6 in the subjects with abdominal obesity, were wrist, WC and WHtR, respectively, while in the normal group, hip circumference and WHtR were the most appropriate predictors for Hcy and hs-CRP. In the normal group, since there was no correlated variable with IL-6, the predictive index could not be ascertained. Investigation of each inflammatory factors in the three groups of normal, abdominal or general obesity, and abdominal and general obesity groups revealed an increasing trend for hs-CRP and IL-6; hence after adjustment for age and sex in the linear regression analysis, an increase about 0.37 ng/mL (CI 95%: 0.24 - 0.48, $P = 2.2 \times 10^{-10}$) in the hs-CRP levels and 0.21 pg/mL (CI 95%: 0.10 - 0.33, $P = 16 \times 10^{-5}$) in the IL-6 levels was observed in the normal weight group compared to subjects with both general and abdominal obesity (Table 1). Comparison of hs-CRP, IL-6, and Hcy of phase 1 and 3 of TLGS in case and control groups was shown in Figure 1.

4. Discussion

In this study, association between abdominal obesity and inflammatory factors, it was found that the hs-CRP and IL-6 serum levels in patients with abdominal obesity were higher than in normal subjects. The most appropriate prognostic indexes for hs-CRP, IL-6, and Hcy were abdominal obesity, WC, WHtR, and wrist circumference, respectively. Previous studies have shown a direct relationship between obesity and serum levels of inflammatory factors. For example, a study by Stelzer et al. (21) indicated a positive correlation between IL-6 and the degree of overweight and obesity and suggested leptin and WHR to the best predictors of IL-6. Probably because the fact that abdominal fat tissue is one of the main sources of production of TNF-α and IL-6 cytokines, which, by stimulating the liver, increase the production of hs-CRP. The findings of a study on the association between hs-CRP and METS components showed that WC is the most appropriate indicator for predicting hs-CRP in the population under study. Other study by Vaya et al. (22) on Spanish adults showed that increased levels of Hcy were associated with abdominal obesity and insulin resistance. Contrary to these results, in the TLGS-related study, Hcy serum level was not correlated with an increase in obesity; an alteration which could be explained by variations in the ratio of adipose/muscle tissue in obese subjects and changes in the amount of oxidation of cells. However, this study emphasized that obesity, especially abdominal obesity, is a low-grade inflammatory disease.

In TLGS-dependent study, in subjects with and without MetS, inflammatory factors were compared in subjects with MetS and normal (after adjustment for age and sex) and a significant increase in the levels of hs-CRP, Hcy, and IL-6 was observed in subjects with MetS. It was also found that risk markers increased significantly in association with increasing numbers of MetS components. Multiple linear regression analysis showed that hip circumference and WHtR are the main independent variables in relation to the level of hs-CRP and IL-6 in subjects with MetS, respectively; a positive relationship between inflammatory factors of hs-CRP, IL-6, and WHtR and a negative association between Hcy and WHtR among the subjects with MetS was also found. WHtR is significantly correlated with all risk factors for obesity and MetS, and in longitudinal studies often acts better than BMI in predicting mortality and morbidity. In addition, WHtR can be more sensitive than WC due to adjustments for different statures and a negative correlation between height and certain metabolic risk factors in different populations. The Yusuf et al (23) in a case-control study conducted with < 300,000 participants, emphasized the importance of the WHtR parameter over BMI and WC for predicting MetS. The association between hip circumference and MetS can be explained by considering the effect of waist circumference. The risk of MetS attributed to the waist circumference might be underestimated, regardless of the effect of the hip circumference. WHtR and hips have already been shown to have an independent and opposite effects on metabolic risk factors. While WHtR has a positive correlation with health risk factors, the hip circumference is negatively correlated, which refers to the supportive effect of the hip circumcision, that is probably the result of a higher amount of lean mass in non-abdominal regions. Hence, for a given WHtR,

Table 1. Correlation Between Inflammatory Markers and Anthropometric/Biochemical Variables Among Subjects with and Without Abdominal Obesity

Variables	Hcy				hs-CRP				IL-6			
	AO		No AO		AO		No AO		AO		No AO	
	r	p	r	p	r	p	r	p	r	p	r	p
Sex	-0.211	0.003[a]	-0.227	0.005[a]	0.168	0.018[a]	0.112	0.169	0.087	0.221	0.092	0.258
Age	-0.007	0.926	0.148	0.068	0.070	0.329	0.346	0.000[a]	0.105	0.140	0.018	0.827
Height	0.200	0.005[a]	-0.111	0.177	-0.181	0.010[a]	-0.209	0.010[a]	-0.139	0.050	-0.035	0.665
Weight	0.081	0.256	-0.020	0.806	0.480	0.505	0.112	0.169	-0.010	0.890	-0.097	0.232
BMI	-0.107	0.133	-0.117	0.149	0.204	0.004[a]	0.288	0.000[a]	0.137	0.053	-0.061	0.452
WC	-0.007	0.918	-0.015	0.849	0.175	0.014[a]	0.312	0.000[a]	0.088	0.214	0.056	0.493
Hip	-0.072	0.310	-0.209	0.010[a]	0.163	0.022[a]	0.239	0.003[a]	0.111	0.120	0.054	0.511
Wrist	0.225	0.001[a]	0.159	0.490	-0.139	0.050	0.094	0.247	-0.065	0.358	-0.126	0.121
WHR	0.010	0.161	0.152	0.060	0.004	0.959	0.166	0.040[a]	-0.043	0.545	0.020	0.803
WHtR	-0.123	0.085	-0.063	0.442	0.233	0.001[a]	0.366	0.000[a]	0.154	0.030[a]	0.068	0.406
FBS	-0.114	0.109	0.105	0.198	0.174	0.014[a]	0.069	0.396	0.123	0.084	-0.146	0.071
TG[b]	-0.103	0.149	0.068	0.436	0.051	0.473	0.284	0.000[a]	-0.054	0.452	-0.034	0.673
TC	0.099	0.163	0.085	0.297	0.150	0.035[a]	0.403	0.000[a]	0.002	0.980	-0.032	0.694
HDL-C	-0.155	0.028[a]	-0.033	0.683	-0.009	0.897	0.109	0.181	0.064	0.372	0.078	0.335
LDL-C	-0.006	0.930	0.750	0.359	0.156	0.029[a]	0.345	0.000[a]	0.013	0.859	-0.056	0.489
TG/HDL-C	0.080	0.260	0.069	0.395	0.004	0.952	-0.004	0.962	-0.048	0.497	-0.082	0.316
TC/HDL-C	0.049	0.491	0.109	0.182	0.098	0.167	0.229	0.004[a]	-0.037	0.605	-0.094	0.247
LDL-C/HDL-C	0.118	0.099	0.098	0.226	0.115	0.110	0.220	0.006[a]	-0.028	0.696	-0.105	0.197
SBP	0.002	0.975	0.091	0.270	-0.004	0.958	0.190	0.020[a]	0.123	0.085	0.007	0.932
DBP[b]	0.005	0.947	0.470	0.566	-0.056	0.433	0.297	0.001[a]	0.081	0.262	-0.099	0.227
Hcy[b] (mmol/L)	-	-	-	-	0.158	0.414	0.021	0.797	-0.007	0.921	-0.103	0.207
hs-CRP[b] (ng/mL)	0.058	0.414	0.210	0.797	-	-	-	-	0.157	0.026[a]	0.014	0.859
IL-6[b] (pg/mL)	-0.007	0.921	-0.103	0.207	0.157	0.026[a]	0.014	0.859	-	-	-	-

Abbreviations: AO, abdominal obesity; BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; Hcy, homocysteine; HDL-C, high density lipoprotein cholesterol; hs-CRP, C-reactive protein; IL-6, interleukin-6; LDL-C, low density lipoprotein cholesterol; r, Pearson correlation (adjusted from ref. 6); SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio.
[a] $P < 0.05$.
[b] Logarithmic transformation.

the higher hip circumference does not indicate a health risk. Using these findings, one can find a way to use WHtR and hip circumference to predict metabolic disturbances. The components of MetS are individual and groups of risk factors for morbidity and mortality. People with MetS are twice as likely to die from cardiovascular disease and three times more likely to have a heart attack or stroke. The intra-abdominal fat plays a major role in cardiometabolic risks. Visceral fat is a metabolically active tissue that produces prothrombotic and pro-inflammatory cytokines. Furthermore, in the Jackson Heart Study, fatty liver and abdominal visceral adipose tissues were independent links of cardiometabolic risks (24).

In investigating the relationship between CRP and CVD, the effect of common CVD risk factors in various models with and without CRP in predicting the incidence of CVD, over a three year follow-up presented that CRP levels predict the incidence of CVD in middle aged Iranians, but not independently from the risk factors of traditional CVD commonly used in clinical settings. In other words, CRP measurements in middle-aged Iranian populations will not improve cardiovascular risk prediction (25). Several cohort studies have shown a high correlation for CRP with an increased CVD risk. In a meta-analysis performed by Danesh et al. (26) it was shown that after adjustment for established CVD risk factors, the adjusted combined multivariate OR for CHD was 1.58 (CI 95%: 1.48 - 1.68). Studies issued after this meta-analysis reported a similar rel-

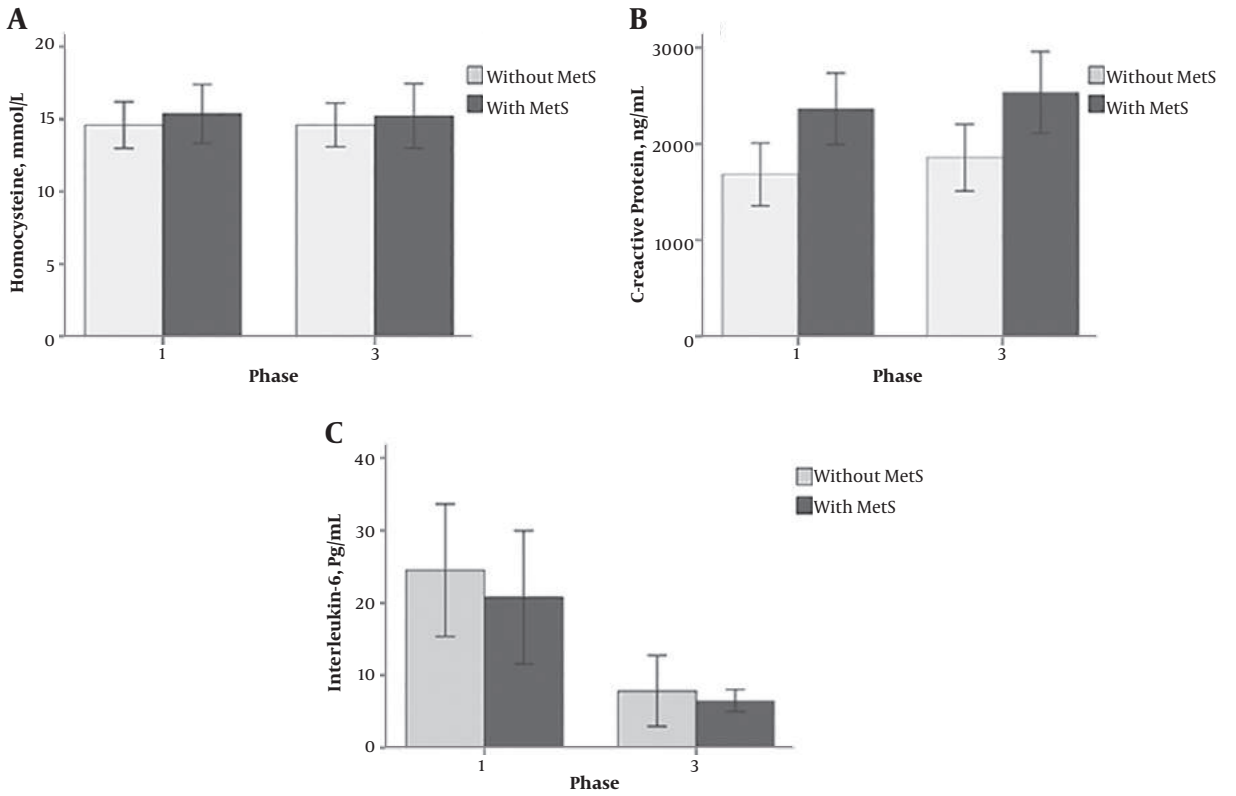

Figure 1. The mean levels of A, homocysteine; B, C-reactive protein; C, interleukin-6 in the subjects with and without MetS in phases 1 and 3 of the TLGS; Error bars: ± SE

ative risk for CRP, except in the study of Rotterdam's elderly population, where high CRP levels were not associated with an increased risk of cardiovascular disease; on the other hand, a moderate but significant correlation was observed between CRP levels and common risk factors of CVD which has also been observed in other studies. Hence, univariate dependence between CRP and CVD can be clarified by the correlation between CRP and other risk factors; CRP significantly contributed to the increased risk of CVD, only regarding status of smoking. This finding is similar to the recent American Heart Association's declaration that measurement of inflammatory factors may help recognize people who most likely benefit from changing their lifestyle. Like most other studies, adding CRP to AUC did not improve Framingham's risk function. These findings confirmed the results of the Rotterdam study that was conducted in an elderly population.

The results of the study on the role of CRP in predicting type 2 diabetes in a TLGS-dependent study showed that increased the levels of CRP was associated with an increased risk of increasing T2D, although this is independent of other diabetes risk factors such as FBS, familial history of diabetes, BMI, and HOMA-IR, so that the OR of having diabetes after adjustment for age of the highest tertile was 3.6 (CI 95%: 1.5 - 8.2, P = 0.001), after adjustment for FBS, familial history of diabetes, BMI, and HOMA-IR, this OR was significantly reduced (OR = 0.8; CI 95%: 0.2 - 2.8, P = 0.8). However, given that CRP had a strong association with BMI, FBS and HOMA-IR, the effect of CRP on prediction of diabetes after adjustment with these variables was not significant. In a study, Festa et al. (27) entitled "insulin resistance atherosclerosis study"; it was found that CRP was not significantly correlated with diabetes after adjusting for BMI and WC. In the MONICA cohort study, to investigate the association between CRP and incident diabetes mellitus among middle-aged men, the OR for diabetes after adjustment for age and survey, associated with the highest CRP quartile was 7.2 times higher than the lowest quartile, which was not statistically significant after adjustment for BMI, cigarette smoking, and SBP (28). There are also studies that reported a strong and independent relationship between CRP and type 2 diabetes, such as a case-control study of Hu et al. (29) in a large population (737 diabetics and 785 control subjects). In the women's health studies with 188 diabetics and 362 controls, by Pradhan et al. (30) CRP was introduced as a predictor of diabetes in women.

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Footnotes

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Diabetes Mellitus: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: We summarized findings from Tehran lipid and glucose study (TLGS) about different aspects of type 2 diabetes (T2D) over the span of nearly 2 decades.
Evidence Acquisition: A review was undertaken to retrieve papers related to all aspects of T2D from the earliest date available up to January 30, 2018.
Results: An annual crude incidence rate of 10 per 1000 person-years of follow-up was found for T2D in adult participants. Overall incidence rate of pre-diabetes/T2D was 36.3 per 1000 person-years or about 1% each year among youth. Diabetes was associated with increased risk of CVD [hazard ratio (HR): 1.86, 95% confidence interval (95% CI): 1.57 - 2.27] and mortality [HR: 2.56; 95% CI: 2.08 - 3.16] in the total population. Compared with non-diabetic men and women, their diabetic counterparts survived 1.4 and 0.7 years shorter, respectively, during 15 years of follow-up. Wrist circumference, hyperinsulinaemia, 25-hydroxy vitamin D and increase in alanin aminotranferase provided incremental prognostic information beyond the traditional risk factors for incident T2D in adults. Using decision tree algorithms, a number of high risk groups were found for incident T2D. A probability of 84% was found for incidence of T2D among a group of men with fasting plasma glucose (FPG) > 5.3 mmol/L and waist to height ratio (WHtR) > 0.56, and women with FPG > 5.2 mmol/L and WHtR > 0.56.
Conclusions: Original TLGS studies have contributed greatly to clarify important evidence regarding the epidemiology and risk factors for T2D among Iranian population.

Keywords: Diabetes, Tehran Lipid and Glucose Study, Cardiovascular Disease

1. Context

Diabetes is a common chronic disease worldwide (1). An estimated 415 million people globally had diabetes in 2015, a rate projected to increase to 642 million people by 2040, with most having type 2 diabetes (T2D) (2). Diabetes poses an increased risk of mortality and morbidity among those who already have it (3). A total of 56.4 million deaths occurred worldwide in 2015, of which, 1.6 million (2.8%) were due to diabetes (4). The Eastern Mediterranean Region (EMR) has the highest prevalence of diabetes in the world, a figure projected to increase in the near future (5, 6). Before the year 2000, a high prevalence of diabetes had been reported in some urbanized populations of Iran (7, 8). In 2005, the first survey of risk factors of noncommunicable diseases of Iran, conducted on 70.981 populations aged 25 - 64 years, found that about 2 million Iranian adults (7.7%) had diabetes, about half of them were undiagnosed; moreover, an additional 16.8%, or 4.4 million, had impaired fasting glucose (IFG) (9).

In 1999, the Tehran lipid and glucose study (TLGS), as the first population based cohort in Iran, was initiated to investigate diabetes, hyperlipidemia, hypertension, obesity, cigarette smoking and other cardiovascular risk factors among a representative population of Tehran, the capital of Iran (10). The prospective observations made over the course of nearly two decades of follow-up have clarified important knowledge regarding the epidemiology and risk factors for diabetes. A large number of investigators from around the Iran have worked with TLGS data and published many articles since 2000. This review briefly presents the key findings from those papers and summarizes several contemporary TLGS publications on different

aspects of T2D.

2. Evidence Acquisition

We searched PubMed, Scopus, Web of Science, and Google Scholar for all relevant studies from the earliest available date to January 30, 2018. The search query included three keywords (diabetes, TLGS and Iran) which were combined with "and".

3. Results

We found a total of 22 articles for inclution in our review. A summary of the findings of the included studies is presented below.

3.1. Prevalence

3.1.1. Youth

Of a total of 3,721 residents aged 10 - 19 years from first and second phases of TLGS, 8 people were diagnosed with type 1 diabetes (T1D) or T2D (11).

3.1.2. Adults

According to data from phase 1 of TLGS (1999 to 2001), among 9,489 Iranian adults aged $\geq$ 20 years, the prevalence of diagnosed and undiagnosed T2D were 8.1% and 5.1% in males, and 10% and 4.7% in females, respectively. Also, the prevalence of isolated IFG [fasting plasma glucose (FPG) of 5.6 - 6.9 and 2-h postchallenge plasma glucose (2h-PG) < 7.7 mmol/L], isolated impaired glucose tolerance (IGT) (2h - PG 7.7 - 11.0 and FPG < 5.6 mmol/L) and combined IFG/IGT were 8.7%, 5.4% and 4.0% in males, and 6.3%, 7.6%, and 4.5% in females, respectively (12).

3.2. Incidence

3.2.1. Youth

During 1999 to 2011, with median of 9.2 years of follow-up, 208 cases of pre-diabetes/T2D occurred among 2,563 subjects, aged 10 - 19 years. Accordingly, overall incidence rate of pre-diabetes/T2D was 9.1 per 1000 person-years or about 1% each year among Iranian youth, aged 10 - 19 years (11).

3.2.2. Adults

During 1999 to 2011 (median follow-up of 9.5 years), among 8,400 (3,620 men) non-diabetic participants of TLGS, an estimated 736 people (433 women and 303 men) > 20 years of age were newly diagnosed with T2D. In the total population, the annual crude and age-standardized incidence rates (95% CI) of T2D were 10.6 (9.92 - 11.4) and 9.94 (7.39 - 13.6) per 1000 person-years of follow-up. The corresponding values were 10.2 (9.13 - 11.4) and 9.36 (5.84 - 14.92) in men, and 11.0 (9.99 - 12.0) and 10.1 (7.24 - 13.9) in women, respectively. The highest incidence rate of T2D was found in men over the age of 80 years (21.8 per 1000 person-years) and women aged 60 - 69 (24.0 per 1000 person-years) (13). In addition, during 1999 to 2012 (median follow-up of 9.5 years), an estimated 1,755 people (853 men and 902 women) > 20 years of age were newly diagnosed with pre-diabetes (combined IFG/IGT, isolated IFG and isolated IGT), with incidence rates of 46.1 and 36.8 per 1000 person-years in males and females, respectively (14).

3.3. Risk Factors

3.3.1. Youth

Multivariate analysis of data from the TLGS found that one standard deviation (SD) increase in FPG and body mass index (BMI) was associated with increased risk of developing pre-diabetes/T2D among adolescents, aged 10 - 19 years, with corresponding hazard ratios (HR) of 1.89 (1.6 - 2.23) and 1.43 (1.08 - 1.90), respectively (11). Also, this study showed that the paternal history of T2D was linked with increased risk for pre-diabetes/T2D in the adolescents [HR: 1.63 (1.02 - 2.60)].

3.3.2. Adults

Data from the TLGS showed that during 1999 - 2008 (median follow-up time of 6 years), risk for developing T2D was 30% higher in females than in males, after adjusting for age; however, there were no significant gender differences in risk of T2D in the multivariate adjusted model. The independent risk factors were age, family history of diabetes, BMI, abdominal obesity, high triglycerides (TG) (TG > 2.2 mmol/L), IFG, Isolated IGT, and combined IFG and IGT (15). Table 1 shows the odds ratio (OR) for above mentioned risk factors derived from the multivariate logistic regression model (15).

On the basis of survival analysis of 8,400 people (3,620 men) from TLGS and a median of 9.5 years follow-up, a significant association was observed for 2h-PG, FPG and family history of diabetes with risk for incident T2D in the total population, with a 42% increased risk per each unit increment of 2h-PG [HR: 1.42 (1.35 - 1.49)] and FPG [HR: 3.39 (2.93 - 3.91)] (13). Family history of diabetes was associated with 64% (1.40 - 1.92) increased risk of T2D in the total population. Moreover, a significant relation was found between the wrist circumference (cm) and incident T2D [HR: 1.16 (1.03 - 1.31)] among women. On the other hand, among men, BMI and low educational status (illiterate/primary school) was associated with the incidence of T2D [HR: 1.12 (1.02 - 1.22) and 1.80 (1.23 - 2.36), respectively] (Table 2) (13).

Further research conducted on the TLGS population showed the potential predictive role of some biomarkers and anthropometric measures for developing T2D. In a

Table 1. Variables Predictive of the Incident Type 2 Diabetes During 6 Years of Follow-Up, Tehran Lipid and Glucose Study[a,b]

Variables	OR (95% CI)	P Value
Age, per 10 years	1.2 (1.1 - 1.3)	0.008
Family history of diabetes	1.8 (1.3 - 2.5)	< 0.001
Body mass index ≥ 30 kg/m²	2.3 (1.5 - 3.6)	< 0.001
Abdominal obesity	1.9 (1.4 - 2.6)	0.001
High triglyceride	1.4 (1.1 - 1.9)	0.04
Glucose tolerance category		
Normal	1	-
Isolated IFG	7.4 (3.6 - 15.0)	< 0.001
Isolated IGT	5.9 (4.2 - 8.4)	< 0.001
IFG/IGT	42.2 (23.8 - 74.9)	< 0.001

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; 2h-PG, 2-h postchallenge plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OR, odds ratio; TG, triglyceride.
[a]The data adapted from "Population-based incidence of Type 2 diabetes and its associated risk factors: results from a six-year cohort study in Iran" (Harati et al.) (15).
[b]Abdominal obesity: Waist circumference greater than 88 cm for women and 102 cm for men. High triglyceride: Triglyceride > 2.2 mmol/L. Isolated IFG: FPG 5.6 - 6.9 and 2h-PG < 7.7 mmol/L. Isolated IGT: 2h-PG 7.7 to 11.0 and FPG < 5.6 mmol/L.

study with a median follow-up of 9.2 years (1999 - 2012), fasting hyperinsulinaemia was found to be a strong risk factor for progression to T2D in adults, aged ≥ 20 years with normal fasting glucose/normal glucose tolerance at baseline. The HR (95% CI) for incident T2D was 2.01 (1.03 - 3.89) and 2.04 (1.22 - 3.40) for fasting hyperinsulinaemia in men and women, respectively (16). In a nested case-control study using data from the TLGS, the relation between 25-hydroxy vitamin D [25(OH) D] and newly diagnosed T2D was examined. Cases were 191 subjects of T2D diagnosed at a median follow-up of 3.6 years. The ORs for T2D were estimated using conditional logistic regression models for tertiles of serum 25(OH) D concentrations [tertile 1: 2.82-11.02 (reference), tertile 2: 11.03 - 21.80, and tertile 3: ≥ 21.82 ng/mL]. Adjusted ORs (95% CI) of T2D were 0.47 (0.25 - 0.90) and 0.43 (0.23 - 0.82), for the second and third tertiles, respectively. Results of cubic spline regression model showed an apparent threshold of ~10 ng/mL for 25(OH) D, below which the risk of newly diagnosed T2D increased dramatically (17). Another nested case-control study on 133 subjects, free of diabetes at baseline, (68 cases and 65 controls) investigated the associations of different hepatic markers including aspartate aminotransferase (AST), alanin aminotranferase (ALT), gamma glutamyl transferase (GGT), insulin and C-reactive protein (CRP) with incident T2D (18). Odds ratios were calculated for each 1 SD increment in hepatic markers; both ALT and GGT were associated with diabetes incidence when adjusted for CRP and insulin. After Further adjustment for anthropometric, blood pressure and metabolic factors, only ALT was associated with T2D incidence [OR: 3.18 (1.02 - 9.86)]. Further analysis found no statistical difference between the area under the receiver operating characteristic curves (AUC) of the models with (AUC 0.820) and without (AUC 0.802) ALT (P = 0.4). This study showed that ALT was associated with incident T2D independent of traditional risk factors; although, its addition to the traditional risk factors did not improve the performance of model (18). In another prospective evaluation with a median follow up of 8.8 years, after controlling for multiple diabetes risk factors, a 1 SD (0.9 cm in males and 1.0 cm in females) increase in wrist circumference was associated with a 17% increase in diabetes incidence in males (P = 0.012) and a 31% increase of diabetes incidence among females (P < 0.001). After controlling for the BMI or waist circumference (WC), wrist circumference was an independent predictor of T2D only among females (19).

3.4. Interactions Between Risk Factors of T2D

Findings of the TLGS also support the concept of a certain type of interaction between risk factors of T2D using decision tree algorithms. Using data from the TLGS, Ramezankhani et al. applied the decision tree approach to identify important risk factors for T2D and exploration of interactions between those factors (20, 21). In a prospective design, they examined 15 and 20 variables for the model development in men and women, respectively, and found 2h - PG, FPG and waist-to-height ratio (WHtR) as the most important predictors for incidence of T2D in both genders (20); age was also found to be a risk factor only among men. The study was noteworthy in that it showed the interaction between those risk factors mentioned above separately for men and women. For example, among men with an FPG ≤ 4.9 mmol/L a 16% probability for incidence of T2D was seen during study period; whereas, a group of men with FPG > 5.3 mmol/L and waist to height ratio (WHtR) > 0.56 had a 84% probability for incidence of T2D. Moreover, a 12% probability for incidence of T2D was found among females who had FPG ≤ 5.2 mmol/L and WHtR ≤ 0.55, and 84% probability for incidence of T2D in a group of women with FPG > 5.2 mmol/L and WHtR > 0.56.

3.5. Cardiovascular Diseases (CVD)

In a study of 7,239 participants (3,246 men), free of CVD at baseline, T2D was associated with 70% (95% CI, 1.36 - 3.53) and more than two folds (1.74 - 2.77) increased risk of non-fatal CVD in men and women, respectively (22). In another study conducted on 8,108 participants (3,686 men), aged ≥ 30 years (23), having T2D significantly increased the risk of developing CVD (HR, 1.86 (1.57 - 2.27) during study period (1999 - 2012). Accordingly, the population attributable fraction (PAF) of diabetes was 13.87%, showing that about 14%

Table 2. Hazard Ratios of Potential Risk Factors for Incidence of Type 2 Diabetes, Tehran Lipid and Glucose Study[a]

Risk Factors	Men	P Value	Women	P Value	Total	P Value
Fasting plasma glucose, mmol/L	3.30 (2.65 - 4.10)	< 0.001	3.54 (2.94 - 4.26)	< 0.001	3.39 (2.93 - 3.91)	< 0.001
2-h postchallenge plasma glucose, mmol/L	1.43 (1.34 - 1.54)	< 0.001	1.43 (1.34 - 1.53)	< 0.001	1.42 (1.35 - 1.49)	< 0.001
Wrist circumference, cm	1.07 (0.91 - 1.26)	0.36	1.16 (1.03 - 1.31)	0.01	1.07 (1.00 - 1.16)	0.04
Family history of diabetes	1.78 (1.39 - 2.29)	< 0.001	1.54 (1.26 - 1.89)	< 0.001	1.64 (1.40 - 1.92)	< 0.001

[a]The data adapted from "Sex specific incidence rates of type 2 diabetes and its risk factors over 9 years of follow-up: Tehran lipid and glucose study" (Derakhshan et al.) (13).

of CVD was attributable to the causal effects of diabetes. Based on TLGS data from 1999 - 2010 (24), the HRs of coronary heart disease (CHD) were 3.9 (2.9 - 5.3) and 2.7 (2.0 - 3.6) in men and women with diabetes, respectively, compared to their non-diabetic peers. The PAF of diabetes was 6.7% for CHD. In another study of 5,198 participants (2,267) of TLGS (25), subjects with known diabetes mellitus (DM), but no history of CHD in either gender [HR, 1.7 (0.9 - 3.3) and 6.2 (3.6 - 10.6) in males and females, respectively)], exhibited a CHD risk comparable to non-diabetics with a history of CHD [2.1 (1.4 - 3.1) and 5.2 (3.2 - 8.3) in males and females, respectively]. Among newly diagnosed DM participants without history of CHD, the risk was comparable to nondiabetics with a prior CHD only among men [1.7 (1.1 - 2.7) vs. 2.1 (1.4 - 3.1)]. In another TLGS study conducted from 1999 to 2009 (26), T2D was associated with a 2.18-fold (95% CI, 1.34 - 3.56) increase in the risk of stroke among 2,378 participants (1,089 men), aged $\geq$ 50 years with a PAF of 22.0% for stroke.

3.6. Mortality

In a prospective analysis of 6,331 individuals, aged $\geq$ 30 years from the TLGS study with 8.6 years of follow-up (1999 - 2009), T2D was associated with increased risk of all-cause death [HR: 2.00 (1.30 - 3.09)] in the total population. The PAF of T2D for all-cause mortality was 10.1%, showing that 10.1% of mortality was attributable to the causal effects of diabetes (27). Analysis of data from the TLGS from 1999 to 2012, of 8,108 participants (4,422 women), aged $\geq$ 30 years and mean follow-up of 10.7 years, showed that T2D continues to be associated with incremental all-cause mortality [HR: 2.56 (2.08 - 3.16)]. Calculations of PAF showed that among the total population, 24.37% of mortality was attributable to the T2D (23). In a multi-state analysis of TLGS data from 1999 - 2014, conducted on 7,239 TLGS participants (3,246 men) aged $\geq$ 30 years, T2D was significantly associated with increased risk of all-cause mortality [2.72 (2.03 - 3.63) and 1.92 (1.37 - 2.67) in men and women, respectively]. A recent study of 1,198 diabetic patients, aged $\geq$ 30 years, with a median follow-up of 10 years, found that during the study period (1999 - 2012), 281 and 172 participants experienced cardiovascular diseases events and all-cause death, respectively; this study showed that FPG level of 7.22 - 10 mmol/L [HR: 1.46 (1.12 - 1.96)], FPG level $\geq$ 10 mmol/L [2.04 (1.53 - 2.72)], hypertension [1.65 (1.28 - 2.13)], hypercholesterolaemia [1.96 (1.40 - 2.75)] and high WHtR ($\geq$ 0.95 for men and $\geq$ 0.90 for women) [1.30 (0.99 - 1.70)] were significant predictors of CVD among diabetic patients. Considering all-cause mortality events, hypertension [1.70 (1.23 - 2.36)], FPG level $\geq$ 10 mmol/L [2.31 (1.55 - 3.20)] and smoking [1.45 (1.03 - 2.04)] were significant predictors (28).

3.7. Prediction of Diabetes

Several risk prediction models for incident T2D have been developed using TLGS data. A simple risk score model was developed using data from a 6-year follow-up of 3,242 TLGS participants, aged $\geq$ 20 years without diabetes at baseline (1999 - 2001). The risk score model was developed by logistic regression model (29), which included systolic blood pressure (SBP), family history of diabetes, WHtR, triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C) $\geq$ 3.5 and FPG level $\geq$ 5mmol l/L. This score-based model was well calibrated (Hosmer-Lemeshow χ^2 test = 6.147, P = 0.631) and the discrimination capability, assessed by the AUC, was 0.83 (95% CI, 0.80 - 0.86); internal validity of this score-based model was assessed by the bootstrap procedure which yielded mean estimated AUC of 0.83 and non-parametrically estimated 95% CI of 0.795 - 0.855 (29). A recent TLGS study (20) developed a series of prediction models using the decision tree method to predict the incidence of T2D among an adult population of 6,647 participants (43.4% men), aged > 20 years. The study population were selected from the first (1999 - 2001) and second phases (2002 - 2005) of TLGS and were followed until 2012; two different models (with and without 2-h PG) were developed using three types of decision tree algorithms separately in men, women and total population. The entire datasets divided into two sets; 70% of the data for model development, and the remaining (30%) for the internal validation. Performance of the models was assessed using sensitivity, specificity, AUC, geometric mean (G-Mean) and the F-Measure. The Quick Unbiased Efficient Statistical Tree (QUEST) algorithm found to have the highest sensitivity (78% in both genders) and G-Mean (0.75% and 0.78% in

males and females, respectively); QUEST showed good discrimination power with AUC > 0.78 in both genders. FPG, 2h-PG, and mean arterial blood pressure (MAP) were the most important factors for incidence of T2D in both men and women. The decision tree models also identified the best cut-off point for each predictor for the best prediction of T2D among participants (20). Although both risk prediction models were internally validated by splitting methods, the external validity of these models have not yet been assessed in a different population.

3.8. Lifestyle Behaviors and Risk of T2D

In a cluster-controlled trial study, the effect of lifestyle intervention on incidence of T2D was assessed among TLGS participants (30). The lifestyle interventions were implemented through educational programs to improve dietary behaviors, increase levels of physical activity, and decrease cigarette smoking. After 3.6 years of intervention, the incidence of T2D was 12.2 and 8.2 per 1000 person-years, in the control and intervention groups, respectively, which showed 65% (95% CI; 30 - 83%) reduction in incidence of T2D in the intervention group compared to controls. Accordingly, lifestyle interventions produced greater improvement in subjects over 65 years of age and in individuals with IFG or IGT.

3.9. Life Expectancy

In a study of 7,239 participants (3,246 men), free of CVD at baseline, the effect of T2D on non-fatal CVD and all cause death, with and without non-fatal CVD, was studied using the multi-state Markov model (22). Also, a 15-year life expectancy (LE) was estimated for participants with and without diabetes; the study found that having T2D significantly increased the risks of developing non-fatal CVD [HR: 1.70 (1.36 - 3.53) and 2.19 (1.74 - 2.77) in males and females, respectively] and of all-cause mortality [2.72 (2.03 - 3.63) and 1.92 (1.37 - 2.67) in males and females, respectively]. After incident non-fatal CVD, the association between diabetes and all-cause death was not significant among women; however, the study found a greater risk of mortality among diabetic men [HR: 2.19 (1.36 - 3.53)]. The 15-year LE, free of non-fatal CVD was 1.7 and 1.4 years longer in non-diabetic men and women, respectively, than their diabetic counterparts ($P < 0.001$). Also, compared with diabetic men and women, their non-diabetic counterparts survived 1.4 and 0.7 years longer, respectively. After a non-fatal CVD, diabetes was associated with 1.3 years decrease in 15-year LE among men (22).

4. Conclusions

This paper summarizes many of the key findings related to T2D including prevalence, incidence, risk factor, and risk prediction models in the TLGS cohorts. We believe valuable information can be gained from these findings bringing us one step closer to developing prioritized programs for prevention and management of diabetes. We should emphasize the fact that in all studies included in this review, diagnosis of diabetes was based on the FPG and 2h-PG, not on the history of self-reported diabetes. Therefore, the accuracy of the results is reasonably high in the TLGS population.

In Iran, there are other cohort studies with similar data (31-34). It is only logical that aggregated data from these studies would yield a large representative database to examine risk factors and develop risk models that are applicable to most, if not all, of the Iran; this is currently underway through the "Iran Cohort Consortium" established in 2016 (35).

Although various aspects of diabetes have been investigated in TLGS, there still remains a number of issues which should be resolved in future researches, one of which is population awareness; it is unclear what proportions of the diabetic populations in TLGS were aware of their condition and what was the increase in awareness during the study period? Another important concern that should be considered in future researches is investigation of the frequency of hospitalizations among diabetic patients of the TLGS study. Also, extensive research is needed to identify how durations of pre-diabetes T2D influence clinical outcomes in TLGS participants. Current evidence suggests that increasing duration of T2D is associated with increasing CVD risk. It has been reported that the relative risk of coronary heart disease (CHD) is 1.38 times higher and the risk for CHD mortality is 1.86 times higher for each 10-year increase in duration of T2D (36). Although extensive observational researches have been conducted in the last decades on TLGS participants, research on genetic causes of T2D is in its infancy (37), which offers a good opportunity to expand our knowledge in relation with T2D in the near future. Lastly, simultaneously with ageing, that affects metabolism, nutrient intake, physical activity, and risk of chronic diseases, it will be critically important to study economical cost of treating T2D and its complications among study populations. We believe that there is a strong need to shift our studies toward randomized controlled trials to provide clinical evidence of the efficacy of the pharmacological treatment of T2D in Iranian populations.

The ultimate aim is that the improved understanding of the mechanisms of T2D and the associated risk factors will permit improved healthcare programs and implementation of new and potentially more efficient preventive strategies, which is critically important for our country with 1% annual incidence rate of T2D.

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Overweight and Obesity: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: The prevalence of overweight and obesity are increasing worldwide and have frequently been associated with health risks. This review highlighted several studies regarding obesity, outlining contributions of over a span of almost two decades in the Tehran Lipid and Glucose Study (TLGS).

Evidence Acquisition: A systematic review was undertaken to retrieve articles related to all aspects of obesity from the earliest available date up to January 30, 2017.

Results: Prevalence of excess weight, including overweight and obesity were 20.8 and 63.6% among those aged below and above 20 years, respectively. TLGS found a high incidence of obesity with higher incidence in women among Tehranian adults; the cumulative incidence of obesity was 31.3, 38.1 and 23.4% for the whole population, women, and men, respectively. In children and adolescents, younger non-obese 7 - 9 years old, compared to 10 - 11 year olds are at greater risk of obesity. Prevalences of abdominal obesity in men and women were 52.8% and 44.4% respectively. Similar to generalized obesity, a high incidence of abdominal obesity was observed; the total cumulative incidence of abdominal obesity was 76.0% (83.6% for men and 70.9% for women). Metabolically healthy obese (MHO) and metabolically healthy abdominal obese (MHAO) are two important obesity phenotypes. People with these phenotypes have different risks for cardiovascular disease (CVD), type 2 diabetes (T2DM), and mortality. In the TLGS participants, MHO was found in 2% and 7.7% of the whole and obese population, respectively, whereas MHAO phenotype was reported in 12.4% and 23.5% of the whole and abdominal obese population. In these unstable conditions, during the long term follow up the metabolic risks developed in nearly half of the individuals. During a 12-year follow-up, incident CVD did not increase in the MHO phenotype compared to metabolically healthy normal weight (MHNW) individuals, but the risk of CVD events had increased in all metabolically unhealthy phenotypes. However in another report, over a 10-year follow-up, MHAO phenotype had an increased risk for CVD in comparison to the reference group, metabolically healthy non-abdominal obese (MHNAO) individuals.

Conclusions: The TLGS studies bridged the significant gap in knowledge regarding prevalence, incidence, trends, morbidities and mortalities for obesity among Iranian population.

Keywords: Obesity, Pediatric Obesity, Abdominal Obesity, Morbid Obesity, Metabolically Benign Obesity

1. Context

Over the past century, obesity and chronic diseases appear as leading health concerns via shared environmental changes (1). Excess weight is major risks for cardiovascular disease (CVD), type-2 diabetes (T2DM) and mortality (2-4), factors favoring a positive energy balance and weight gain over several decades include increasing per capita high-calorie and palatable food consumption, substitution of occupational physical activities with sitting works with electronic devices, decreasing time spent in leisure-time physical activities and growing time for watching television, and growing use of medicines that have weight gain as a side effect (5, 6).

In this report, we aim to review the 20 year findings of the Tehran Lipid and Glucose Study (TLGS) on obesity and overweight.

2. Evidence Acquisition

We searched MEDLINE (via PubMed) for articles published between Jan 1, 2000, and Jan 1, 2018, using the search terms ("obesity" OR "overweight" OR "waist circum-

ference" OR "body mass index" AND "Tehran Lipid and Glucose Study". All articles with the terms "obesity or overweight" in their title, subject or MeSh were included for initial review. Since studies with nutrition or chronic kidney diseases (CKD) issue as their main topic have been addressed elsewhere, we excluded all articles that have examined the relationship between obesity and nutrition or CKD from this review.

2.1. Definition of Overweight and Obesity

For adults, *overweight* is defined as $25.0 \leq$ BMI ≤ 29.9 kg/m^2, and *obese* is defined as BMI $\geq$ 30.0 kg/m^2. Obesity is classified by grade as follows: $30 \leq$ BMI ≤ 34.9 (class I), $35 \leq$ BMI ≤ 39.9 (class II), and BMI $\geq$ 40 (class III) (7). By WHO definition *obesity* is defined as BMI-for-age > 2 SD and *overweight* is defined as 1 SD < BMI-for-age $\leq$ 2 SD in each gender for children (8).

On the other hand, waist circumference (WC) is used to classify excess adiposity which is also associated with increased cardiovascular risk. Iranian National Committee of Obesity defined WC $\geq$ 90 cm as at risk for CVD and WC $\geq$ 95 cm as high risk for CVD events for both sexes (9).

3. Results

3.1. Youth

3.1.1. Prevalence

In Phase I (1998 to 2001), in children and adolescents aged 3 - 19 years, the overall prevalence of excess weight (including overweight and obesity) was 20.8% based on value BMI-for-age $\geq$ 1 SD in each gender. The prevalence of excess weight for age group 2 to 5, 6 to 11 years and 12 to 19 years were 13, 19.2 and 23.5%, respectively. By gender, no significant differences have been reported in prevalence of excess weight.

In addition, obesity prevalence among adolescents with less educated parents was higher than adolescents with high educated parents.

According to data documented between 1998 - 2001 (Phase I), the prevalence of sever obesity which defined as BMI for-age $\geq$ 3 SD was 1.2% for children and adolescents (aged 3 to 19 years). This prevalence rose to 3% between 2013 - 2016 (Phase V).

3.1.2. Incidence

Another analysis of TLGS data, with a median 8.7 years of follow-up showed that among children, aged 7 - 11 years the incidence of obesity was 17% (CI: 14.7 - 20.3), which in boys was higher than girls [19.5% (CI: 15.4 - 24.8) vs. 14.5% (CI: 10.9 - 19.1)]. Compared to non-obese children 10 - 11 years old, 7 - 9 years old were at higher risk of obesity, supported by a cumulative incidence of obesity of 22% in the younger subgroup, compared with only 10.8% in older children (Figure 1). The best childhood obesity predictors were overweight, WC more than 95th percentile, hypertension, MetS, and parental obesity (10).

3.1.3. Trends

According to TLGS data, between Phases I (1999 - 2001) to Phase IV (2009 to 2011) overall obesity prevalence in youth, aged 3 to 11 years, was increased from 5.5% to 9.4%. Using GEE (generalized estimating equation) analysis, relative risk of obesity was calculated, comparing each phase to its previous phase: Phase II in reference to Phase I (RR = 1.06, CI: 1.04 - 1.08), Phase III in reference to Phase II (RR = 1.01, CI: 1.00 - 1.03) and Phase IV in reference to Phase III (RR = 0.96, CI: 0.94 - 0.98). Between group difference was significant in all subgroups (age, gender, parental obesity) except for parental education. For children aged below 7 years old in phase I, trend of obesity throughout the study was higher, compared to those $\geq$ 7 years of age in this phase.

3.1.4. Morbidity

According to TLGS data, the incidence of MetS during 6.6 years follow-up in 6 - 12-year-old children was 10.7% which was higher in boys compare to girls. Higher BMI and WC were associated with higher incidence and prevalence of MetS and both of these anthropometric indices had the similar power in predicting MetS. Among children aged 6 - 12-years the cut-off values to predict MetS for BMI were 16.5

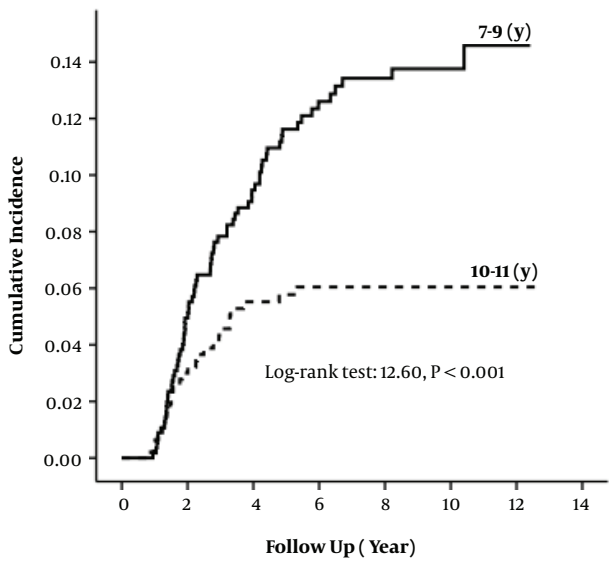

Figure 1. Kaplan-Meier curve for cumulative incidence of obesity (BMI $\geq$ 30 kg/m^2) in different age groups in Tehranian children

kg/m^2 and 16.3 kg/m^2; for WC were 57.5 cm and 56.5 cm for boys and girls, respectively (11).

During a 10.2 year follow-up of 1100 participants with aged 11 - 18 years and without MetS at baseline, the cumulative incidence of MetS in early adulthood for men was 25.5% and for women was 1.8%. In boys, WC and waist-to-height ratio (WHtR) had the highest risk for the MetS. In age group 11 - 14-year, the results did not change after adjustment for BMI in addition to WC (OR for WC: 2.28 without BMI adjustment vs. 1.98 with BMI adjustment). Therefore, these results showed that beyond BMI, WC predict the risk of MetS. On the other hand, the anthropometric indices did not have significant associations with subsequent MetS risk in girls. Therefore we can conclude that in Tehranian male adolescents abdominal obesity (WHtR and WC) compare to BMI were better predictor for early adulthood MetS (12).

In another study, did not report any association with the risk of MetS in adulthood after adjustment for BMI in adult age, MetS in adolescent age and overweight or obesity. AUC was greater for obesity than MetS (0.619 vs. 0.589). Thus, it seems that independent of adult BMI, adolescent MetS or obesity did not predict early adult MetS (13).

Another analysis was done to explore the association between childhood BMI status (3 - 11 years) and adulthood dysglycemia over a median 9.3 years follow up. The results showed that considering individual and parental factors together, BMI status in early life stages is not associated with the incidence of adult dysglycemia.

3.2. Adults

3.2.1. Prevalence

In Phase I the overall prevalence of obesity was 23.3% (29.6 and 14.6% in women and men, respectively). Overweight was present in 38.3% of women and 42.4% of men. In both sexes, the highest rate of obesity was observed in the 50 - 59 year age group. The prevalence of obesity in both sexes increased with age up to 60 years (14).

The prevalence of abdominal obesity in women was greater than men (76.7 vs. 36.5%) (15).

3.2.2. Incidence

Cumulative incidence of obesity among Tehranian adults in a median 8 year follow up were 31.3, 38.1 and 23.4% for the whole population, women, and men, respectively. In both sexes, higher risk for development of obesity were higher BMI or WC, MetS and lower educational level at baseline. Men showed the highest incidence rate during their 20s and women during their 40s (Figure 2) (16).

In an investigation with a median 6 years of follow up, total cumulative incidence of abdominal obesity for total population was 76.0% (83.6% for men and 70.9%, for women).

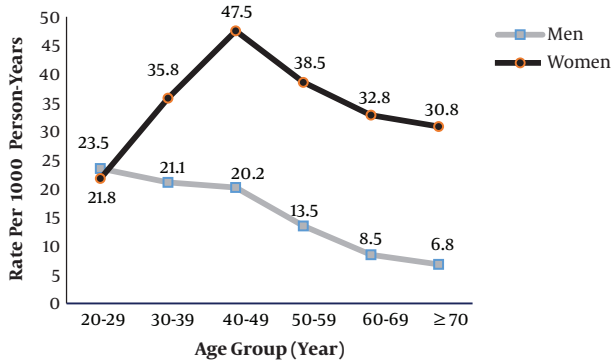

Figure 2. Incidence rates of obesity according to age and sex in Tehranian adults

3.2.3. Trends

In both genders, obesity and abdominal had increasing trends across four phases of TLGS in all study subgroups of adults with using generalized estimating equation (GEE) models. The crude prevalence of obesity and abdominal obesity at baseline were 23.1 and 47.9 %, respectively. These values increased to 34.1 and 71.1 %, at the end of follow-up. Over the whole study period, risks of obesity increased for men and women (RR = 1.6, CI: 1.5 - 1.8 and RR = 1.2, CI: 1.2 - 1.3, respectively) and abdominal obesity for men and women (RR = 1.5, CI: 1.4 - 1.5 and RR = 1.2, CI: 1.2 - 1.3, respectively). Regardless of age, marital status and educational level, these rising trends were observed in all subgroups (Figure 3) (17).

3.2.4. Obesity Phenotype

Reports on risk factors for related health outcomes in different obesity phenotypes have yielded contradictory results. A combination of BMI groups and metabolic status developed to different obesity phenotypes; including metabolically obese but normal weight (MONW) and metabolically healthy but obese (MHO). These phenotypes have different risks for incidence of T2DM, CVD and mortality in further (18). Recently, some studies have also used waist circumference (WC) for definition of obesity phenotype.

Prevalence of MHO (based on having less than one component of metabolic syndrome) was 2% in the total population and 7.7% in the obese population (19).

Accordingly, the MHAO phenotype (based on abdominal obesity and having less than one component of metabolic syndrome) found in 12% and 23% of the total population and the abdominal obese population, respectively (20).

Our investigations showed the MHO phenotype is an unstable condition and half of the individuals developed

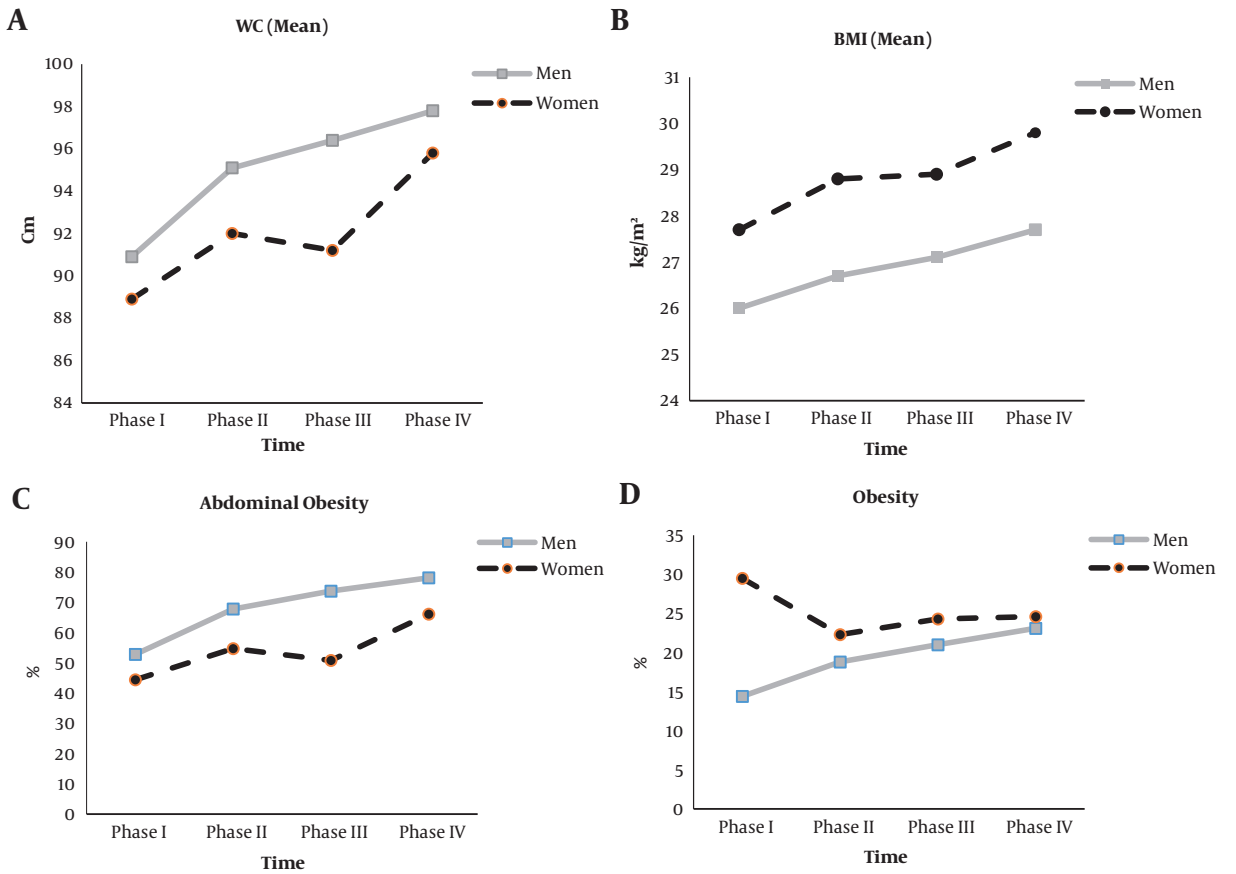

Figure 3. Adult mean levels of (A) waist circumference (WC), (B) body mass index (BMI), (C) prevalence of abdominal obesity, and (D) obesity, across different phases of TLGS

to MetS during 10 years of follow-up (21). Moreover, after 10 years follow-up 43.3% of MHAO adults lost their metabolic health, of whom 42.1% developed MetS (22).

During 8.1 years of follow-up, normal-weight subjects with MetS or T2DM compared to overweight and obese subjects without MetS or T2DM had a significantly higher CVD event rate. Also, within the group with MetS or T2DM, a significant association between BMI and CVD events has been observed, whereas no significant association was shown within the group without MetS or T2DM (23).

Moreover, in another report during amount one decade, incident or cardiovascular events did not increase in MHOW and MHO compared to MHNW individuals; however all metabolically unhealthy phenotypes (having more than one metabolic components) showed increased risk of CVD events (Table 1) (19).

Our reports during a 10-year follow-up in different abdominal obesity phenotypes (having less than one metabolic component) showed that the risk for CVD was higher in MHAO and MUNAO compared to the reference group; metabolically healthily non-abdominal obese (MHNAO) (20). On the other hand, another study showed that in the MHAO phenotype all-cause mortality risk was not greater than reference group (HR = 1.3, CI: 0.9 - 2.0) (24).

Moreover, the association between different obesity phenotypes and incident T2DM was assessed in our cohort. Women with normal weight and MetS compared to healthy normal weight women had ORs for T2DM incidence of 8.8 (CI: 3.7 - 21.2). This values for men were 3.1 (CI: 1.3 - 7.0) (25).

In another report, during 12 years of follow-up the results of multivariate models showed that T2DM risk was increased in all unhealthy abdominal obesity phenotypes (having more than one metabolic component) except the metabolic unhealthy non-abdominal obesity (MUNAO) phenotype in men. Also, MHAO phenotype was associated with incident of T2DM in men (HR = 1.5 CI: 1.0 - 2.4) and in women (HR = 1.7 CI: 1.1 - 2.6) (26).

Table 1. Hazard Ratios for Incident of CVD During 12-Year Follow-up According to Baseline Obesity Phenotypes[a]

	Healthy Metabolic Status			Unhealthy Metabolic Status		
	Normal Weight (MHNW) (n = 1218)	Overweight (MHOW) (n = 731)	Obese (MHO) (n = 147)	Normal Weight (MUNW) (n = 920)	Overweight (MUOW) (n = 2429)	Obese (MUHO) (n = 1722)
Unadjusted HR (95% CI)	1	0.8 (0.5 - 1.3)	1.0 (0.5 - 2.3)	2.8 (2.1 - 3.9)[d]	2.9 (2.1 - 3.8)[d]	2.5 (1.9 - 3.4)[d]
Model 1 (95% CI)[b]	1	1.2 (0.8 - 1.9)	1.8 (0.8 - 4.0)	1.9 (1.4 - 2.7)[d]	2.4 (1.8 - 3.2)[d]	2.6 (1.9 - 3.6)[d]
Model 2 (95% CI)[c]	1	1.2 (0.7 - 2.0)	1.7 (0.7 - 4.4)	1.7 (1.2 - 2.4)[d]	2.0 (1.5 - 2.8)[d]	2.4 (1.7 - 3.5)[d]

Abbreviations: CVD, cardiovascular disease; MHNW, metabolically healthy normal weight; MHO, metabolically healthy obese; MHOW, metabolically healthy over weight; MUHOW: metabolically unhealthy overweight; MUNW, metabolically unhealthy normal weight; MUO: metabolically unhealthy obese.
[a] Metabolic health was defined as one or less of metabolic syndrome components.
[b] Adjusted for age and sex.
[c] Adjusted for model 1 plus smoking, education level, physical activity, family history of premature coronary artery disease and total cholesterol.
[d] Compared to reference group (MHNW), P < 0.001.

4. Conclusions

This review summarizes most of the key findings of the TLGS cohort related to obesity, including prevalence, incidence, trend, and obesity phenotype during 20 years. Overall, similar to other developing countries, we are faced with a high prevalence of obesity and abdominal obesity especially in adulthood. Moreover, the longitudinal nature of TLGS has provides an opportunity to confirm the simultaneous alarming rise of obesity and abdominal obesity, underscoring the urgent need for implement action of preventive strategies aimed of reducing the burden of the problem.

Although a prospective population based study such as TLGS, sheds more light on the various aspects of obesity and its related risk factors, there still remain a certain number of issues which should be resolved in future research. First, considering the limitations of anthropometric indices, we need to gather data regarding body compositions. Second, in order to assess the impact of socioeconomic status on different aspects of obesity, more information is needed to determine this variable. Third, to obtain a bigger picture of the problem at a national level, we can merge our findings with the results of other cohorts in Iran. Fourth, research on genetic causes of all types of obesity and related comorbidities must be conducted in the future. Also, in the context of assessing the impact of obesity during adolescence on cardiovascular outcomes in early adulthood, providing some surrogate endpoint such as intimal media thickness can overcome the problem of low event rate in this age category.

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Serum Lipids During 20 Years in the Tehran Lipid and Glucose Study: Prevalence, Trends and Impact on Non-Communicable Diseases

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Abstract

Context: Dyslipidemia, including elevated serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and triglycerides (TG), and low high density lipoprotein cholesterol (HDL-C) is a major modifiable risk factor for non-communicable diseases (NCDs). This review summarizes many of the key findings on lipid measures in the Tehran lipid and glucose study (TLGS), a large scale community-based study with an approximately two decade follow-up.

Evidence Acquisition: A systematic literature search was conducted using PubMed, Scopus, Web of Science databases, and the library of the Research Institute for Endocrine Sciences, using the following keywords: Lipid measures, lipid ratios, lipid profile, dyslipidemia, and "Tehran lipid and glucose study". Articles were categorized based on fields of prevalence, trends, and impact of lipid profile on incident NCDs and mortality.

Results: Between 1999 - 2001, the prevalence of high risk lipids ranged from 14% (low HDL-C) to 17% (high LDL-C) among adolescents, although among adults the lowest and highest prevalence were observed for low HDL-C (19%) and high TG (28%). Despite favorable trends for lipid parameters among adolescents, adults, and the elderly population, a considerable number of diabetic individuals, failed to achieve the optimum level of serum lipids. During follow-up, consumption of lipid-lowering drugs increased from 1.5 to 9.0% and 3.7 to 11.4% among adult men and women, respectively. The association between different lipid parameters and related ratios for incident type 2 diabetes (T2D), hypertension, metabolic syndrome and cardiovascular diseases differed between genders. Interestingly, each 1-unit increase in TC/HDL-C increased risk of hypertension among women (odds ratio (OR): 1.19, 95% confidence interval (CI): 1.00 - 1.27) and T2D among men (OR: 1.27, 95% CI: 1.06 - 1.51). Moreover, TC, LDL-C, non-HDL-C, Ln-TG, TC/HDL-C, and Ln-TG/HDL were inversely associated with non-cardiovascular mortality.

Conclusions: Despite high prevalence of high risk lipid profiles among the TLGS population at baseline, favorable trends were observed in levels of all lipid components, which might be attributable to increased consumption of lipid-lowering medications and improvement in the general knowledge of Iranians regarding limited consumption of hydrogenated oil. Considering the impact of lipid profiles on incident NCDs, more attention should be paid to at-risk groups for screening and treatment purposes.

Keywords: Dyslipidemia, Lipid Profile, Trends, Hypertension, Metabolic Syndrome, Diabetes, Cardiovascular Disease, Mortality

1. Context

Metabolic risk factors including dyslipidemia are considered as the most important determinants of non-communicable diseases (NCDs) worldwide as reported by the global burden of disease (GBD) studies (1). Dyslipidemia, including elevated serum levels of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and triglycerides (TG) as well as low serum level of high density lipoprotein cholesterol (HDL-C), is considered as an important modifiable risk factor for NCDs including hypertension (HTN), type 2 diabetes (T2D) and mortality worldwide (2). Moreover, dyslipidemia has a major contribution in the development of coronary heart disease (CHD) (3) and cerebrovascular outcomes (4); there is a well-established correlation between lipid levels and cardiovascular diseases (CVD) (5-7). The relationship between dyslipidemia and atherosclerosis as a preceding pathologic condition in the development of both cardiac and cerebrovascular diseases (8), has been a field of active research over the last century, as the prevalence of atherosclerosis and associated cardiovascular (CV) complications increase in the industrialized world (9).

Heterogeneous patterns in the prevalence of dyslipidemia, its relation to CVD and all-cause mortality rates, and response to lipid-lowering drugs have been observed in different countries (10), providing important data that could explain the variation of CVD burden and its risk factors in different ethnicities.

Tehran lipid and glucose study (TLGS) as a large scale and long term community-based cohort study, was initiated in 1999 to investigate NCDs including dyslipidemia and its associated risk factors among a representative population of Tehran, the capital of Iran. The large number of prospective investigations conducted over almost two decades of follow-up, providing essential information on the prevalence and trends of abnormal lipid profiles as well as the association between different lipid profiles and incident NCDs. The purpose of this review is to summarize data from several TLGS publications and present their key findings regarding different aspects of dyslipidemia.

2. Evidence Acquisition

A comprehensive review of the literature was conducted, using the following keywords in conjunction with the term 'Tehran lipid and glucose study' to search literature published until December 2017: Lipid measures, lipid ratios, lipid profiles, lipid levels, and dyslipidemia. We searched these keywords in the title, abstract, and text using international databases, including PubMed, Scopus, and Web of Science; we also searched among published articles within framework of the TLGS, archived in the library of the Research Institute for Endocrine Sciences. Authors reviewed all articles and excluded those that did not meet the inclusion criteria. After reviewing all abstracts, articles in English language focusing on the fields of prevalence, trends, and impact of lipid profiles on incident NCDs and mortality were included in the study. Among the acquisitioned manuscripts, 24 articles were included in the study to be thoroughly reviewed and extract study details. Two reviewers critically evaluated all papers independently and data was extracted by 1 reviewer and rechecked by a second one.

3. Results

3.1. Prevalence of High Risk Levels of Lipids in the TLGS

3.1.1. Adolescents

Among 3148 participants (1447 males and 1701 females), aged 3 - 19 years at baseline of the TLGS (1999 - 2001), mean levels of TC, TG, LDL-C and HDL-C in girls were 4.47, 1.22, 2.77 and 1.16 mmol/L, respectively; corresponding values for boys were 4.32, 1.16, 2.64 and 1.16 mmol/L, respectively, indicating that girls had higher mean levels of TC, TG and LDL-C than boys. Regarding changes in lipid profiles in different age groups, results showed that level of serum TG increased gradually and reached a peak at the age of 17 - 19 years of age for boys and 11 - 13 years for girls; HDL-C levels were at their highest between 7 - 10 years of age in both genders and decreasing thereafter; LDL-C in both genders tended to increase and reach to a peak between 7 - 10 years of age, decreasing thereafter. Appendix 1 in Supplementary File illustrates the prevalence of abnormal lipid profiles among this group using national cholesterol education program (NCEP) criteria for high TC and high LDL-C and the 90th percentile of concentration of serum TG and 10th percentile for HDL-C.

According to findings of the TLGS, Tehranian children and adolescents had higher levels of TC, LDL-C and TG and lower level of HDL-C as compared to other study populations (11).

Based on the NCEP cut off points, another study conducted among older adolescents, aged 14 - 19 years, the prevalence of high levels for serum TC, LDL-C, and TG and low HDL-C in males, were 12.1, 12.9, 26.1 and 34.2%, respectively, while corresponding values in females were 15.1, 17.9, 21.4 and 25.0%, respectively (12).

3.1.2. Adults

According to baseline data of the TLGS (1999 to 2001), among 6246 participants (2339 males and 3907 females), aged 20 - 64 years, mean level of serum TC was significantly higher in women than in men (5.51 vs. 5.33 mmol/L) and increased with ageing. Twenty-four percent of the population had high TC level, defined as TC $\geq$ 6.19 mmol/L (20% of men and 26% of women); the prevalence of high TC level increased with age in both genders, with women having 2-fold higher prevalence of high TC than that observed in men, aged $\geq$ 45 years (Appendix 2 in Supplementary File) (13).

Unlike TC, men had significantly higher serum TG level than women (2.15 vs. 1.83 mmol/L). Although women showed increasing level of serum TG by ageing, the mean level of serum TG in men aged between 35 - 44 years peaked to 2.40 mmol/L and decreased thereafter. Twenty-eight percent of the total population had high risk levels of TG, defined as $\geq$ 2.26 mmol/L. Although the prevalence of high risk TG levels increased continuously with ageing among women, the corresponding prevalence in men reached a plateau around mid-adulthood (35 - 64 years of age), a difference much bigger in participants aged between 25 - 34 years, with approximately a 2-fold higher prevalence in men (33% vs. 14%). However, in those aged between 55 - 64

years, prevalence of high risk serum TG levels was higher in women.

Mean levels of serum LDL-C in both genders were almost similar, except for those aged > 45 years, in whom the corresponding value for women was higher than men; furthermore LDL-C levels increased with ageing in both genders. Twenty-three percent of population were in the high risk range of LDL-C, defined as ≥ 4.14 mmol/L (20% of men and 24% of women); prevalence of high risk LDL-C increased with age up to 64 years in both genders. Among participants between 45 - 64 years of age, women had a higher prevalence of being at risk than men (13).

Moreover, as shown in Appendix 2 in Supplementary File, mean serum levels of HDL-C were overall lower in men than in women (1.01 vs. 1.16 mmol/L) and remained almost constant with age in both genders. The prevalence of HDL-C level in high risk range (below 0.91 mmol/L) were higher in men than in women in all age groups with corresponding values of 30 and 13% in male and female participants, respectively (13).

3.2. Trends of High Risk Levels of Lipids in the TLGS

3.2.1. Adolescents

According to the data for adolescents from three phases of the TLGS (1999 - 2001, 2002 - 2005, and 2006 - 2008), mean serum levels of TC, TG, LDL-C and HDL-C decreased from 1999 - 2001 to 2006 - 2008 in both male and female participants, aged 15 - 19 years. Moreover, among participants aged 10 - 14 years, mean TC, LDL-C, and HDL-C levels decreased from 1999 - 2001 to 2006 - 2008 in both genders, whereas mean level of TG showed significant decrement only among females. Although the prevalence of high TG level did not change during the three time periods in boys or girls, aged 10 - 14 years, the prevalence of high TC, high LDL-C, and low HDL-C among boys, and the prevalence of high LDL-C among girls were significantly decreased. Furthermore, among participants, 15 - 19 years of age, both genders showed significant decrease in prevalence of high TC and high LDL-C (Table 1) (14).

3.2.2. Adults

During over a decade long follow-up of 4951 adult participants, in both age and multivariate-adjusted analyses statistically significant decreases were shown in mean serum levels of TC, TG and LDL-C and increase in mean levels of serum HDL-C for both genders as well as significant decrease in the prevalence of high serum levels of TC, TG, non HDL-C, and low levels of HDL-C. Prevalence of high lipid ratios including TG/HDL-C and TC/HDL-C also decreased (Figure 1 and Table 2). These results remained unchanged even after excluding participants with prevalent CVD or using lipid-lowering medications. Moreover, consumption of lipid-lowering drugs increased from 1.5 to 9.0 % and 3.7 to 11.4% during follow-up of adult men and women, respectively (15). It has been indicated that diabetic patients of the TLGS population gained significantly better control of their serum LDL-C levels compared to non-diabetic participants and percentage of the subjects who achieved the targeted levels of serum lipids, excluding HDL-C, increased over time in both genders, predominantly in the diabetic group. This study showed that among CVD risk factors, high TC caught the most attention of healthcare professionals in Iran (16).

3.2.3. Elderly

The results of study for the 1490 elderly population, mean age 67 years, revealed that serum levels of TC, TG, non-HDL-C, and LDL-C decreased significantly over about 9 years of follow-up; in contrast, the HDL-C level of participants rose during the same period. Furthermore, the prevalence of low HDL-C and high levels of TG, non-HDL-C, and LDL-C showed a decreasing trend in both genders. Likewise, consumption of lipid-lowering drugs demonstrated a prominent increasing trend from 4% at baseline to 26% at the last follow-up among men; corresponding values for women were 10 and 41%, respectively (17).

3.2.4. Seasonal Variation of Lipid Parameters

At baseline, the cross sectional phase of TLGS (1999 - 2001), seasonal variability in lipid parameters was noted. Among men, mean levels of TC and LDL-C were higher in winter than in summer, the coldest and hottest seasons, respectively (5.35 vs 5.17 mmol/L for TC, and 3.44 vs 3.26 mmol/L for LDL-C). Among women, mean levels of TG were significantly higher in summer (1.95 mmol/L) than in winter (1.56 mmol/L). Regarding prevalence of dyslipidemia among the total population in different seasons, there was 4.8% increase in hypercholesterolemia and 25.8% increase in high LDL-C in winter, compared to summer, increments which were higher in men than in women. Furthermore, an overall decrement of 17.7% in the prevalence of hypertriglyceridemia was observed only among women in winter (18).

3.3. Impact of Lipid Profiles and Related Ratios on Incident NCDs

3.3.1. Hypertension

Among 2831 Tehranian adult women during a median follow-up 6.4 years, in multivariate models, the odds ratios of a 1 standard deviation (1-SD) increase in TG, TG/HDL-C and TC/HDL-C increased the risk of HTN by 16, 18 and 19%, respectively; however, the corresponding change for serum HDL-C level was associated with 14% lower risk (Table 3) (19). Also, considering progression from pre-HTN to HTN, a 1-SD

Table 1. Trends of Serum Lipid Parameters and Prevalence of High Risk Levels of Each Lipid Component in Adolescents (1999 - 2008)[a,b]

Age Groups (y)	1999 - 2001		2002 - 2005		2006 - 2008	
	Mean Level (mmol/L)	Prevalence of High Risk Level (%)	Mean Level (mmol/L)	Prevalence of High Risk Level (%)	Mean Level (mmol/L)	Prevalence of High Risk Level (%)
Boys						
10 - 14						
TC	4.32	14.2	4.22	10.7	4.19	8.5
TG	1.00	5.3	1.09	7.9	0.93	4.0
LDL-C	2.64	15.1	2.56	12.1	2.46	8.8
HDL-C	1.16	36.1	1.09	44.9	1.21	25.2
15 - 19						
TC	4.16	12.4	3.75	4.0	3.72	3.7
TG	1.10	9.3	1.04	5.5	1.03	8.9
LDL-C	2.53	11.7	2.28	5.7	2.15	3.6
HDL-C	1.04	55.5	0.97	64.3	1.03	54.1
Girls						
10 - 14						
TC	4.42	15.9	4.11	9.8	4.14	11.8
TG	1.21	9.4	1.14	8.8	1.07	5.7
LDL-C	2.69	14.9	2.46	9.1	2.46	10.1
HDL-C	1.10	44.3	1.06	48.8	1.13	35.5
15 - 19						
TC	4.37	16.0	3.96	6.6	3.98	8.7
TG	1.03	4.7	0.91	1.7	0.95	4.1
LDL-C	2.69	17.6	2.46	11.0	2.35	7.7
HDL-C	1.14	40.2	1.06	47.4	1.14	35.9

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.
[a] High risk level was defined as $\geq$ 5.2 mmol/L for TC, $\geq$ 2.26 mmol/L for TG, $\geq$ 3.38 mmol/L for LDL-C, and < 1.04 mmol/L for HDL-C.
[b] Data were derived from the Hosseini-Esfahani et al. findings (14).

increase of serum HDL-C decreased the risk of progression by 7%, only among women (20).

Furthermore, during an approximately 10 year follow-up of 1579 adolescent subjects, aged 10 - 19 years, it was shown that among lipid parameters, each 1 mmol/L increase of serum TC level raised the risk of incident HTN by 39% (24).

3.3.2. Metabolic Syndrome

Regarding components of metabolic syndrome, the results of a 9.3 year follow-up of 1611 adult participants showed that high serum TG level predicted development of metabolic syndrome, in the multivariate analysis in the presence of homeostasis model assessment of insulin resistance (HOMA-IR), with hazard ratios (HRs) of 1.89 and 2.87 among men and women, respectively; corresponding values for low HDL-C were 1.62 and 2.16, respectively (25).

3.3.3. Type 2 Diabetes and Pre-Diabetes

Over a median follow-up of 6.4 years of 5201 adults aged $\geq$ 20 years, logistic regression analysis demonstrated positive association between serum TG level and incident T2D in the fully adjusted model among men; each 1-SD increase in serum TG raised the risk of T2D by 23%. In women, HDL-C and TG were independent predictors of developing diabetes; each 1-SD increase in level of HDL-C decreased risk of T2D by 25%, and a 1-SD increase in TG resulted in 36% increased risk of T2D in the fully adjusted model. Regarding lipid ratios, among men, both TG/HDL-C and TC/HDL-C were independent predictors of incident T2D, and any 1-SD increase in TG/HDL-C and TC/HDL-C increased risk of T2D by 25 and 27%, respectively. However, in women, only TG/HDL-C created higher risk for future T2D; each 1-SD increase in TG/HDL-C resulted in 39% increased risk of T2D in the fully

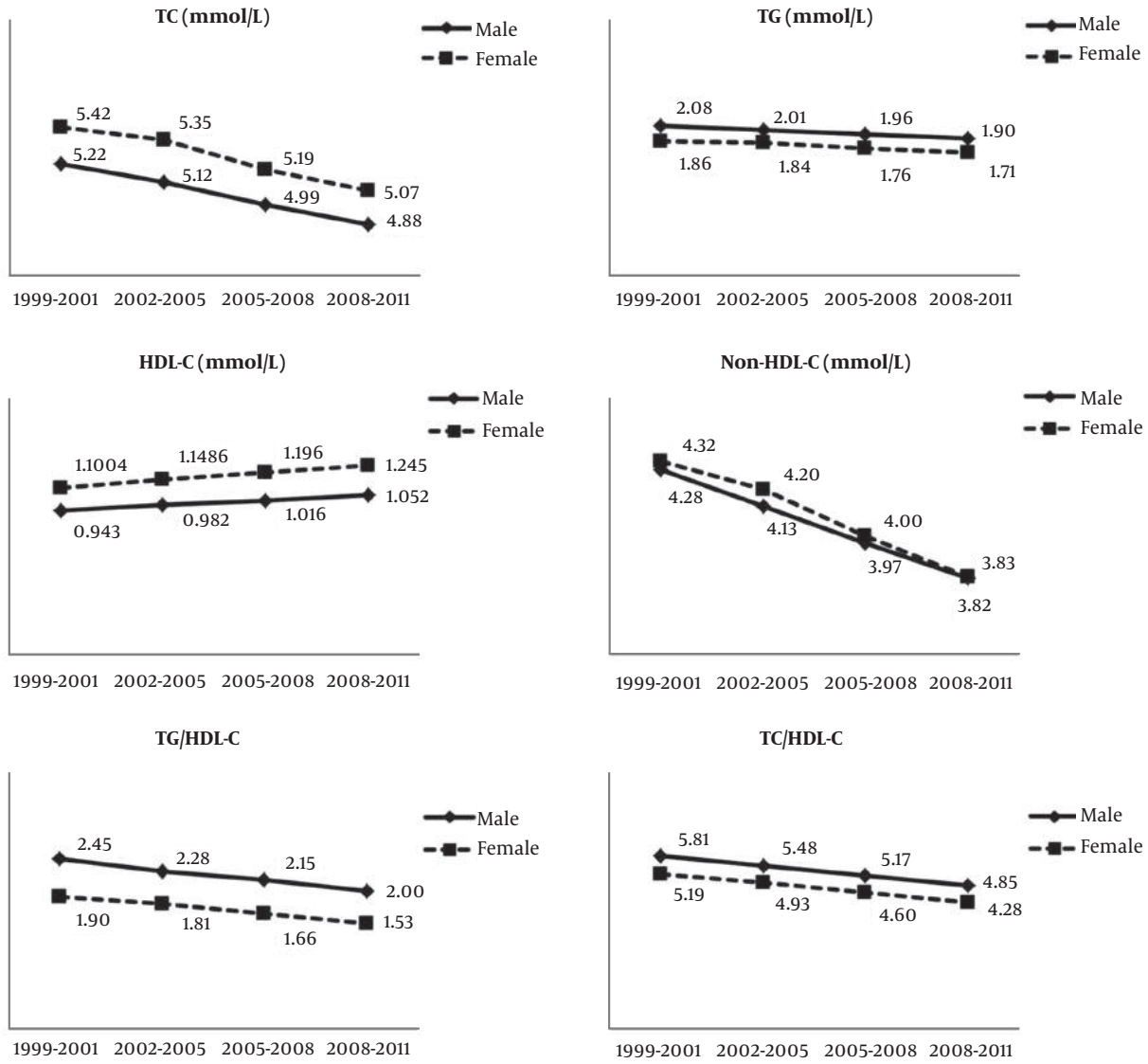

Figure 1. Age-adjusted mean levels of lipid parameters during 10 years follow-up in adults. Data were derived from the Kheirandish et al. findings (15). Abbreviations: HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

adjusted model (Table 3) (21). Moreover, during approximately 10 years of follow-up, using Cox regression analysis, among TG, HDL-C and TC, only TG was shown to be a marginally significant predictor among men (HR with 95% confidence interval (CI): 1.06 (0.99 - 1.13)) (26).

It has been also shown that TG/HDL-C is an independent predictor of pre-diabetes and insulin resistance, increasing the risk of incident pre-diabetes by 11% among women and raising the risk of developing insulin resistance by 7% and 13% among men and women, respectively, in multivariate analyses (27, 28).

3.3.4. Cardiovascular Diseases

3.3.4.1. Cerebrovascular Events

Data from the TLGS showed that during a median follow-up of 9.1 years, none of the lipid profiles components were associated with increased risk of stroke. However, after excluding hemorrhagic stroke, TC, LDL-C and non-HDL-C were found to increase the risk of ischemic stroke among women by 40, 51 and 36%, respectively, in multivariate analysis (Table 3) (22).

Table 2. Trends of Serum Lipid Parameters and Prevalence of High Risk Levels of Each Lipid Component During 10 Years Follow-Up in Adults (1999 - 2011)[a,b,c]

Variables	1999 - 2001		2002 - 2005		2005 - 2008		2008 - 2011	
	Mean Level	Prevalence of High Risk Level (%)	Mean Level	Prevalence of High Risk Level (%)	Mean Level	Prevalence of High Risk Level (%)	Mean Level	Prevalence of High Risk Level (%)
Men								
TC (mmol/L)	5.21	18.1	5.13	15.2	5.00	11.8	4.88	9.4
TG (mmol/L)	2.11	33.7	1.96	29.1	1.93	27.2	1.94	26.5
LDL-C (mmol/L)	3.82	NA	3.73	NA	3.58	NA	3.43	NA
HDL-C (mmol/L)	0.95	71.0	0.97	67.8	1.01	61.2	1.06	53.6
Non-HDL-C (mmol/L)	4.26	19.9	4.15	16.2	3.98	12.1	3.82	9.0
TG/HDL-C	2.43	32.2	2.31	39.4	2.15	34.1	2.00	29.7
TC/HDL-C	5.77	41.3	5.52	34.4	5.18	26.0	4.84	19.1
Women								
TC (mmol/L)	5.42	24.5	5.37	22.5	5.18	17.2	5.07	14.1
TG (mmol/L)	1.88	26.6	1.80	24.4	1.71	21.3	1.74	21.9
LDL-C (mmol/L)	3.90	NA	3.81	NA	3.61	NA	3.46	NA
HDL-C (mmol/L)	1.10	45.4	1.15	40.6	1.03	33.1	1.25	26.5
Non-HDL-C (mmol/L)	4.31	22.9	4.22	19.7	3.98	13.6	3.82	10.2
TG/HDL-C	1.88	28.0	1.82	26.8	1.63	21.8	1.54	19.5
TC/HDL-C	5.20	26.7	4.95	21.8	4.57	14.8	4.28	10.6

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NA, not available; TC, total cholesterol; TG, triglycerides.
[a] High risk level was defined as $\geq$ 6.19 mmol/L for TC, $\geq$ 2.26 mmol/L for TG, $\geq$ 5.15 mmol/L for non-HDL-C, and $<$ 1.04 mmol/L for HDL-C, $\geq$ 2.18 for TG/HDL-C, and $\geq$ 5.97 for TC/HDL-C.
[b] Values are adjusted for age, propensity score, examination cycle, body mass index, current smoking, hypertension, diabetes and TC (in analyses of HDL-C and TG), using covariates from the examination in question.
[c] Data were derived from the Kheirandish et al. findings (15).

3.3.4.2. Coronary Heart Disease

Regarding CHD outcomes, findings indicated that all of the lipid profile components were independent predictors of CHD. Multivariate sex adjusted HRs of CHD for TC, Ln TG, HDL-C, LDL-C, non-HDL-C and TC/HDL-C were 1.16, 1.27, 0.59, 1.23, 1.19 and 1.14, respectively; corresponding results in each gender are shown in Table 3 (22).

Based on survival analysis of 3778 women from the TLGS (1351 postmenopausal and 2427 premenopausal women) with 9.6 years of follow-up, during the premenopausal period, risk of CHD increased due to a 2-fold increase in HDL-C level, which was marginally significant (HR: 2.67 (0.98 - 7.29)); the issue indicates the importance of dysfunctional HDL-C in terms of quality of HDL-C in place of quantity. However, as expected, the hazard of CHD during postmenopausal period was inversely associated with HDL-C level (HR: 0.76 (0.63 - 0.92)) (29).

TG/HDL-C ratio was also demonstrated to be an independent predictor for CHD in a population of Iranian men. It has been shown that men in the top quartile of TG/HDL-C ($>$ 6.87), as compared to the first quartile ($<$ 2.78), had a 75% elevated risk of CHD (HR: 1.75 (1.02 - 3.00)), hence TG/HDL-C can be considered in the assessment of CHD risk (30).

Considering the impact of changes in lipid profiles over approximately 3 years, we found that each mmol/L increase in concentrations of TC, TG, non-HDL-C, TG/HDL-C and TC/HDL-C during follow-up, elevated the risk of CHD by 18, 16, 19, 10 and 10%, respectively. Our findings also emphasized that sustained dyslipidemia increased risk of incident CHD by 67% (31).

3.3.4.3. Cardiovascular Diseases

For short term prediction of CVD outcomes i.e. over 3 years of follow-up, there was no superiority in predictability of LDL-C, non-HDL-C and TC/HDL-C compared with TC (32). Furthermore, over a median 8.6 years of follow-up among 1021 diabetic and 5310 non-diabetic individuals, aged $\geq$ 30 years, adjusted HRs to predict CVD, except for HDL-C, TG and TG/HDL-C, were significant for all lipid measures in diabetic males, being 1.39, 1.45, 1.36 and 1.16 for TC,

Table 3. Odds Ratios/Hazard Ratios and 95% Confidence Interval of Lipid Measures for Predicting Non-Communicable Disease by Gender[a]

Variables	Hypertension[b]		Diabetes[c]		Ischemic Stroke[d]		Coronary Heart Disease[d]		Cardiovascular Disease[e]	
	OR	95% CI	OR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Men										
TC	NA	NA	1.11	0.93 - 1.33	0.78	0.55 - 1.11	1.22[f]	1.07 - 1.39	1.30[f]	1.18 - 1.43
LDL - C	NA	NA	NA	NA	0.82	0.56 - 1.22	1.26[f]	1.07 - 1.48	1.33[f]	1.2 - 1.46
HDL - C	NA	NA	0.91	0.75 - 1.09	1.04	0.24 - 4.47	0.71	0.38 - 1.33	0.94	0.84 - 1.04
TG	NA	NA	1.23[f]	1.02 - 1.49	0.71	0.33 - 1.51	1.23	0.92 - 1.64	1.10[f]	1.0 - 1.21
Non - HDL - C	NA	NA	1.14	0.95 - 1.37	0.78	0.55 - 1.11	1.27[f]	1.11 - 1.45	1.32[f]	1.20 - 1.45
TG/HDL - C	NA	NA	1.25[f]	1.03 - 1.52	NA	NA	NA	NA	1.1	1.0 - 1.21
TC/HDL - C	NA	NA	1.27[f]	1.06 - 1.51	0.87	0.69 - 1.09	1.14[f]	1.05 - 1.23	1.17[f]	1.09 - 1.25
Women										
TC	1.02	0.89 - 1.16	0.94	0.80 - 1.12	1.40[f]	1.08 - 1.82	1.12	0.99 - 1.26	1.21[f]	1.1 - 1.34
LDL - C	NA	NA	NA	NA	1.51[f]	1.06 - 2.15	1.21[f]	1.04 - 1.41	1.22[f]	1.11 - 1.35
HDL - C	0.86[f]	0.75 - 0.98	0.75[f]	0.64 - 0.89	2.27	0.58 - 8.91	0.49[f]	0.27 - 0.90	0.91	0.82 - 1.02
TG	1.16[f]	1.01 - 1.33	1.36[f]	1.13 - 1.58	1.66	0.71 - 3.86	1.34	0.97 - 1.86	1.24[f]	1.1 - 1.4
Non - HDL - C	1.06	0.93 - 1.20	1.01	0.86 - 1.19	1.36[f]	1.04 - 1.78	1.15[f]	1.02 - 1.30	1.23[f]	1.12 - 1.36
TG/HDL - C	1.18[f]	1.04 - 1.35	1.39[f]	1.17 - 1.64	NA	NA	NA	NA	1.22[f]	1.09 - 1.38
TC/HDL - C	1.19[f]	1.00 - 1.27	1.14	0.99 - 1.31	1.13	0.89 - 1.43	1.15[f]	1.06 - 1.26	1.26[f]	1.13 - 1.4

Abbreviations: CI, confidence interval; HDL-C, high density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; NA, not available; OR, odds ratio; TC, total cholesterol; TG, triglycerides.
[a] Multivariate-adjusted OR/HR, with 95% CI were calculated for each 1 standard deviation or 1 mmol/L increase in the value of each lipid parameter and 1 unit increase for lipid ratios.
[b] According to the Tohidi et al. findings (19).
[c] According to the Hadaegh et al. finding (21).
[d] According to the Tohidi et al. findings (22).
[e] According to the Ghasemzadeh et al. findings (23).
[f] Shows statistical significance.

LDL-C, non-HDL-C and TC/HDL-C respectively. In diabetic women, only TC/HDL-C had significant risk of 31%. Among non-diabetic men, all lipid measures, except for TG, were independent predictors for CVD; however, a 1-SD increase in HDL-C significantly decreased the risk of CVD by about 17%. In non-diabetic women, TC, LDL-C, non-HDL-C and TG were independent predictors. Of note, according to our data analysis, HDL-C did not have a protective effect for incident CVD among Iranian diabetic population (33).

During about 12 years follow-up, in multivariate sex-adjusted analysis, each 1-SD increase in TC, LDL-C, non-HDL-C, Ln-TG, TC/HDL-C and Ln-TG/HDL-C was associated with 26, 27, 22, 15, 18 and 14% increased risk of CVD, respectively; however, a 1-SD increase in HDL-C level was found to be related 7% lower risk (P = 0.07). The corresponding results in each gender are shown in Table 3 (23).

In a prospective analysis of 8108 participants, aged $\geq$ 30 years, conducted with the aim of examining the correlation between potentially modifiable risk factors with CVD outcomes during 10.7 years of follow-up, hypercholesterolemia and low HDL-C level played significant roles for incident CVD. In fact, after ranking different potential risk factors of CVD, hypercholesterolemia and low HDL-C level ranked second and fourth, with population attributed fractions (PAF) of 16.7 and 12.3%, respectively (34).

3.3.5. Mortality Events

A study of 5518 individuals, aged $\geq$ 40 years in the TLGS, with a median follow-up of 11.9 years, showed that TC, LDL-C, non-HDL-C, and TC/HDL-C, only in sex-adjusted analysis, significantly increased risk of CV mortality by about 16%, associations that did not remain significant after further adjustment for other risk factors (Table 4). However, among different lipid measures, only TC $\geq$ 6.14 mmol/L was independently correlated with a 43% increased risk of CV mortality (23).

Interestingly, increase in TC, LDL-C, non-HDL-C, Ln-TG, TC/HDL-C, and Ln-TG/HDL-C were significantly correlated with lower risk for non-CV mortality (23). Also it was shown that hypertriglyceridemia (TG $\geq$ 1.69 mmol/L) was correlated with lower risk of all-cause mortality (34), an inverse

Table 4. Hazard Ratios of Lipid Measures for Predicting Cardiovascular and Non-Cardiovascular Mortalities[a]

Variables	Cardiovascular Mortality[b]		Non - Cardiovascular Mortality[b]	
	HR	95% CI	HR	95% CI
TC	1.08	0.96 - 1.21	0.76[c]	0.66 - 0.87
LDL-C	1.08	0.96 - 1.21	0.75[c]	0.66 - 0.86
HDL-C	1.02	0.9 - 1.15	1.07	0.94 - 1.21
TG	0.97	0.85 - 1.10	0.81[c]	0.7 - 0.93
Non-HDL-C	1.02	0.91 - 1.15	0.73[c]	0.64 - 0.84
TG/HDL-C	0.97	0.85 - 1.10	0.83[c]	0.72 - 0.95
TC/HDL-C	1.06	0.95 - 1.20	0.77[c]	0.67 - 0.89

Abbreviations: CI, confidence interval; HDL-C, high density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.
[a] Multivariate-adjusted HR, with 95% CI were calculated for each 1 standard deviation or 1 mmol/L increase in the value of each lipid parameter and 1 unit increase for lipid ratios.
[b] According to the Ghasemzadeh et al. findings (23).
[c] Show statistical significance.

association between lipid measures and non-CV/all-cause mortality events in our studies could be due to residual effects of other conditions such a malnutrition, inflammation, sarcopenia and socioeconomic factors (23, 34).

4. Conclusions

This review has summarizes many of the key findings on lipid measures in the TLGS. There was high prevalence of abnormal lipid profiles and related mean values among adolescents and adults in 1999 - 2001. Despite the high prevalence of abnormal lipid profiles and increasing trends of obesity, sedentary lifestyle, and Westernization of dietary habits, favorable trends were observed in all lipid levels among adolescents, adults, and the elderly population, which could hardly be attributable to increase in consumption of lipid-lowering drugs. It has been shown that more than 30% of families in Iran are now consuming less saturated oil than they did before, the finding that possibly explains these favorable changes of lipid parameters (35, 36). Importantly, despite of these favorable trends, a considerable number of people viz. diabetic subjects did not achieve the targeted levels of serum lipids. Based on this large population based cohort, impacts of different lipid parameters and related ratios on incident NCDs including T2D, HTN, metabolic syndrome and CVD differed between genders. We also demonstrated that TC, LDL-C, non-HDL-C, Ln-TG, TC/HDL-C, and Ln-TG/HDL had negative associations with non-CV mortality.

Although various aspects of lipid profiles have been investigated in the TLGS, data related to better understanding the mechanisms and risk factors contributing to dyslipidemia and its associated outcomes, e.g. T2D, HTN, CHD, stroke, and mortality are limited viz. genetic assessment as used in the Mendelian randomization study (37). Moreover, there is ongoing need for high quality studies ensuring efficacy of preventive strategies and pharmacological treatments.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

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Footnote

Authors' Contribution: Aidin Baghbani-Oskouei, Maryam Tohidi and Farzad Hadaegh wrote the article; Aidin Baghbani-Oskouei, Maryam Tohidi, Samaneh Asgari and Azra Ramezankhani carried out the literature search and participated in data collection; Fereidoun Azizi and Farzad Hadaegh participated in the final approval of the version to be submitted. All authors read and approved the final manuscript.

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Blood Pressure and Hypertension: Findings from 20 Years of the Tehran Lipid and Glucose Study (TLGS)

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Abstract

Context: Hypertension (HTN) is a well-known modifiable risk factor for cardiovascular disease (CVD), chronic kidney disease and mortality. Positive effects of blood pressure (BP) lowering for prevention of CVD and death have been documented in several meta-analyses of randomized controlled trials.
Evidence Acquisition: This review focuses on the key findings derived from the Tehran lipid and glucose study (TLGS) papers on different aspects of BP and HTN.
Results: A prevalence of 23% for HTN has been reported in the TLGS population, aged $\geq$ 20 years. Over a decade long follow-up, the crude incidence rate (95% CI) of new-onset HTN defined as systolic BP (SBP) $\geq$ 140 mmHg and/or diastolic BP (DBP) $\geq$ 90 mmHg, and not using antihypertensive medication was 33.63 (32.0 - 35.3) per 1000 person-years. Age, baseline SBP and body mass index were significant risk factors for development of isolated systolic HTN; regarding isolated diastolic HTN, baseline DBP and waist circumference were recognized as important risk factors whereas age, female gender and marriage were shown to be protective factors. SBP decreased significantly in both diabetic and non-diabetic participants; DBP showed a non-significant decrease in diabetic men and a statistically significant decrease in non-diabetic men. Among women, both those with and without diabetes (DM) generally experienced statistically significant decreases in DBP. Cox proportional hazard models showed that neither SBP nor DBP were associated with incident DM in the total population and in either gender, separately. All BP components were associated with CVD and all-cause mortality in the middle-aged population. Contribution of HTN to cerebrovascular events was also documented in the TLGS participants, aged $\geq$ 50 years.
Conclusions: Several important findings regarding BP/HTN have been derived from the TLGS. According to data regarding the prevalence and incidence of preHTN and HTN and their contribution to cardiovascular morbidity and mortality in the TLGS population as a representative sample of Tehranian population, it is recommended that interventions be prioritized for lifestyle modifications for the prevention and appropriate management of preHTN/HTN.

Keywords: Blood Pressure, Hypertension, Prehypertension, Type 2 Diabetes, Cardiovascular, Mortality

1. Context

Hypertension (HTN) as a well-known modifiable risk factor (RF) for cardiovascular disease (CVD), chronic kidney disease and mortality (1), is one of the most prevalent non-communicable diseases worldwide. The overall prevalence of HTN was reported to be 26.4% in 2000 (2), and 24.1% in men and 20.1% in women in 2015 (3), and is estimated to reach 29.2% by 2025 (2). Data from the Iranian survey of risk factors of non-communicable diseases (SuRFNCD)-2011 reported that 25.6% and 39.8% of adults, aged 25 - 70 years had HTN and preHTN, respectively (4).

Associations of systolic and/or diastolic HTN with increased risk of CVD and mortality has been reported in several observational studies (5, 6). Positive effects of BP lowering for prevention of CVD and death have been documented in several meta-analyses of RCTs (7, 8).

This review focuses on the key findings derived from the Tehran Lipid and Glucose Study (TLGS) data documented on different aspects of blood pressure (BP) and HTN.

2. Evidence Acquisition

All TLGS articles related to BP parameters and/or HTN were searched using PubMed, Scopus and Web of Science

with appropriate keywords since January 1999 up to December 2017.

3. Results

3.1. Prevalence

Table 1 shows mean ± SD of SBP and DBP also prevalence of hypertension in different age groups studied in the TLGS phase 1.

3.2. Incidence and Predicting Risk Factors of HTN

During a median follow-up of 6 years, 4656 individuals with 26,846 person-years were followed; new onset HTN events were documented in 805 individuals. Incidence rate of HTN (per 1000 person-years) was 29.3 [95% confidence interval (CI) 26.7 - 32.1]) and 30.9 (95% CI 27.8 - 34.3) for women and men, respectively. Age [HR (95% CI): 0.904 (0.826 - 0.990)], waist circumference (WC) [HR (95% CI): 1.014 (1.006 - 1.023)], diastolic BP (DBP) [HR (95% CI): 1.042 (1.025 - 1.060)], systolic BP (SBP) [HR (95% CI): 0.985 (0.950 - 1.021)], and family history of premature CVD [HR (95% CI): 1.625 (1.235 - 2.137)] predicted incident hypertension in females, while age [HR (95% CI): 1.136 (1.039 - 1.241)], DBP [HR (95% CI): 1.027 (1.010 - 1.044)], SBP [HR (95% CI): 1.086 (1.046 - 1.127)] and smoking [HR (95% CI): 1.264 (0.983 - 1.626)] were shown as predictors in males (12).

During a median 9.5 year follow-up (F/U) of the TLGS population (13), the crude incidence rate (95% CI) of isolated systolic hypertension (ISH) in the total population was reported to be 5.7 (5.0 - 6.5) per 1000 person-years of F/U. The highest incidence of ISH among age categories was observed in the older population (≥ 60 years), at 37.5 (30.6 - 46.0) per 1000 person-years, compared to younger adults (aged 20 - 39 years), at 0.8 (0.5 - 1.3) per 1000 person-years of F/U. The crude incidence rate (95% CI) of isolated diastolic hypertension (IDH) was 10.9 (10.0 - 12.0) per 1000 person-years. The incidence of IDH was higher in subjects aged 40 - 59 years, at 13.67 (11.8 - 15.8) per 1000 person years, and a lower rate was observed in the population aged ≥ 60 years, at 6.4 (3.8 - 10.9) per 1000 person-years of F/U. The crude incidence rate (95% CI) of new-onset HTN defined as SBP ≥ 140 mmHg and DBP ≥ 90 mmHg, and not using antihypertensive medication, was 33.63 (32.0 - 35.3) per 1000 person-years; the crude incidence rate for both high SBP and DBP was 6.3 (5.6 - 7.0) per 1000 person-years. In this study, age, baseline SBP and body mass index (BMI) were significant RFs for development of ISH; regarding IDH, baseline DBP and WC were identified as important RFs whereas age, female gender and marriage were shown to be protective factors (13).

3.3. Incidence and Predicting Risk Factors of Prehypertension

Based on the results of a study by Hadaegh et al. during median F/U of 9.2 years, 1440 new cases of preHTN (735 women and 705 men) were identified and the incidence rate was 593/10000 person-years (95% CI: 564 - 625). The incidence rate of preHTN among women [489/10000 person-years (95% CI: 455 - 526)] was significantly lower than men [764/10000 person-years, (95% CI: 709 - 822)], (P < 0001). During a median F/U of 5.9 years, 872 (432 women and 440 men) individuals had new events of preHTN, resulting in an incidence rate of 546/10000 person-years (95% CI: 511 - 584); incident rates for women and men were 443/10000 (95% CI: 404 - 487) and 715/10000 (95% CI: 651 - 786) person-years, respectively. Participants who developed incident preHTN were older and had higher numbers of cardiovascular RFs in both genders (14). Age, BMI and SBP were significant predictors of preHTN in the TLGS population and also in the sex-adjusted analysis. In both males and females, incident preHTN developed in those who were older, had higher body mass index (BMI), SBP, DBP, triglyceride (TG), total cholesterol (TC), fasting plasma glucose (FPG), and homeostasis model assessment-insulin resistance (HOMA-IR), but who had lower eGFR; 2-hour post-challenge plasma glucose (2h-PCPG) was an independent predictor only in men [HR (95% CI): 1.06 (1.01 - 1.12)], while waist-to-hip ratio (WHpR) and DBP were significant predictors only in women [HRs (95% CIs): 1.24 (1.11 - 1.39) and 1.04 (1.03 - 1.06), respectively]. Also, in the sex-adjusted model, female gender showed lower risk for incident preHTN [HR (95% CI): 0.81 (0.69 - 0.94)] Incident preHTN developed in women with lower HDL-C, compared to the non-incident group (14).

3.4. Dietary Intake of Nitrate and Nitrite and the Risk of Hypertension

In a median 5.8 year F/U of 2799 adults aged ≥ 20 years, multivariate logistic regression model was used to calculate the odds ratios of HTN across tertile categories of residual energy-adjusted NO_3^- and NO_2^- intakes. Mean (SD) intakes of dietary NO_3^- and NO_2^- were 455 (188) and 9.4 (3.6) mg/day, respectively. Overall, no significant relationship was found between dietary intake of $NO3^-$ and the risk of HTN. The highest intake (median intake ≥ 12.7 mg/day) of dietary NO_2^- was associated with reduced risk of HTN in comparison to the lowest tertile category (median intake < 6.04 mg/day) with an odds ratio (OR) of 0.58 (95% CI = 0.33 - 0.98; p for trend = 0.054) in a fully adjusted model (15).

Table 1. SBP, DBP and Prevalence of HTN of Different Age Groups in Phase I TLGS[a,b,c]

Age, y	SBP			DBP			HTN [% (95% CI)]		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
3 - 19[d]	-	-	-	-	-	-	12.7 (11.3 - 14.1)	10.9 (9.6 - 12.2)	11.7 (10.8 - 12.6)
10 - 14[e]	103 ± 11	102 ± 11	-	69.5 ± 9	70 ± 10	-	-	-	-
15 - 19[e]	110 ± 12	106 ± 11	-	72.3 ± 9	72.9 ± 9	-	-	-	-
≥ 20[d]	120 ± 17	116 ± 17	-	77 ± 11	77 ± 10	-	20.4 (19.2 - 21.6)	25.1 (24 - 26.2)	22.9 (22.1 - 23.7)
≥ 60[f]	136 ± 23	141 ± 23	138 ± 23	80 ± 13	82 ± 12	81 ± 12	42.5	51.7	47
60 - 64[f]	134 ± 23	138 ± 22	136 ± 22	82 ± 13	83 ± 12	83 ± 12	38.4	49.8	44.7
65 - 69[f]	137 ± 24	141 ± 23	139 ± 24	80 ± 12	82 ± 12	81 ± 12	42.9	50.7	46.6
≥ 70[f]	139 ± 22	144 ± 23	141 ± 22	78 ± 14	80 ± 11	79 ± 13	46.9	57.1	51.1

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; TLGS, Tehran lipid and glucose study.
[a] SBP and DBP (mmHg) are expressed as mean ± SD.
[b] High SBP/DBP in children and adolescents was defined as values ≥ 95th percentile for sex, age, and height, i.e., the recommended cut points of the National Heart, Lung, and Blood Institute.
[c] Hypertension in adults was defined as mean SBP ≥ 140 mmHg, mean DBP ≥ 90 mmHg, or current treatment with antihypertensive medications either at the time of interview or in the previous one month.
[d] Reference (9).
[e] Reference (10).
[f] Reference (11).

3.5. Predictors of early Adulthood Hypertension

In the TLGS, 1579 subjects, aged 10 - 19 years were considered to evaluate the effects of adolescent anthropometric indices and some cardio metabolic risk factors on the development of adult HTN during 10 years of F/U (16). During F/U, 65 out of 1579 individuals developed HTN in their adulthood, indicating a cumulative incidence of 0.04 (95% CI: 0.03 - 0.05). Of these, 5 individuals were using antihypertensive drugs and 92.3% had systolic and/or diastolic HTN as unknown hypertensive subjects. Individuals who developed early adulthood HTN were one year older at baseline and had higher BMI, WC, wrist and hip circumferences, SBP, DBP, TGs and TC.

3.6. Trend of BP and HTN

In 6181 participants, including 1045 individuals with DM, sex-stratified generalized estimation equation models were used to investigate trends of CVD risk factors during a decade long F/U from TLGS phase 1 to phase 4 (17). SBP decreased significantly in both diabetic (age-adjusted mean SBP of 134.81 and 137.92 mmHg in phase 1 vs. mean SBP of 130.27 and 130.32 mmHg in phase 4 for men and women, respectively) and non-diabetic participants (mean SBP of 120.97 and 118.51 mmHg in phase 1 vs. mean SBP of 118.12 and 111.74 mmHg in phase 4 for men and women, respectively). DBP showed a non-significant decrease in diabetic men and a statistically significant decrease in non-diabetic men. Among women, both individuals with and without DM generally experienced statistically significant decreases in DBP. Regarding BP control, both diabetic and non-diabetic men did not have any statistically significant changes in the BP control rates; however, women demonstrated 1.46 (27.67% to 40.43%) and 1.05 (82.94% to 87.58%) fold increases in the rate of BP control in diabetic and non-diabetic subjects, respectively (17). Figure 1 shows the age-adjusted prevalence of reached BP goal for diabetic and non-diabetic men and women.

In a study by Hosseini-Esfahani et al. (10) data from 3 phases of the TLGS on 10 - 19 y/o adolescents was analysed to assess trends of CVD risk factors in this age group. Based on the findings of this study, mean SBP and DBP decreased from 1999 - 2001 to 2006 - 2008 in both age groups (10 - 14 year and 15 - 19 year) and both genders. In 10 - 14 y/o males, prevalence of high DBP and in 15 - 19 y/o ones, prevalence of high SBP decreased significantly over time. In females, prevalence of high DBP decreased significantly in both age groups.

Finally, regarding the older population of the TLGS, sex-stratified generalized estimation equation models were fitted in 1490 subjects, aged ≥ 60 years. During 8.76 years, age-adjusted mean SBP remained stable, while DBP levels increased in both genders. Meanwhile, the age-adjusted prevalence of HTN showed a remarkable upward trend in both genders, from 43% to 56% in men and 57% to 71% in women. However, at the end of F/U, 35% of hypertensive men and 23% of hypertensive women were not using antihypertensive medications (18).

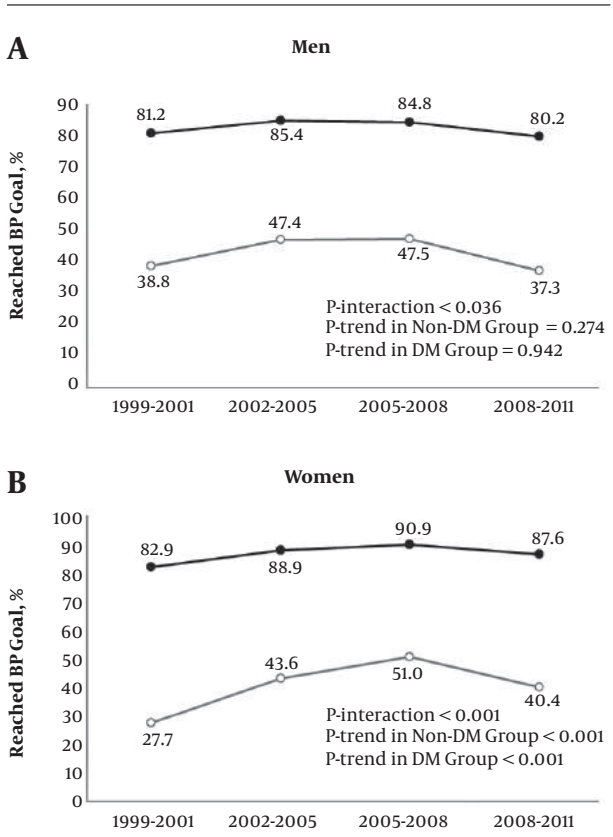

Figure 1. Age-adjusted prevalence of controlled hypertension among diabetic and non-diabetic men and women in phases I-IV of the TLGS. Age-adjusted prevalence of controlled hypertension for diabetic and non-diabetic men (A) and women (B) were derived from data presented by Jahangiri-Noudeh, et al. (17). White circle = diabetic group; black circle = non-diabetic group; BP goal: systolic BP < 140 mmHg and diastolic BP < 90 mmHg (< 80 mmHg in diabetic subjects). DM, diabetes mellitus; BP, blood pressure; phase I (1999 - 2001), phase II (2002 - 2005), phase III (2005 - 2008), phase IV (2008 - 2012); TLGS, Tehran lipid and glucose study.

3.7. Blood Pressure, Insulin Resistance and Type 2 Diabetes

Findings of a decade long study showed that neither SBP nor DBP were associated with insulin resistance and β-cell dysfunction in both genders (19). Likewise, both SBP and DBP were not determined as potential RFs for the incidence of prediabetes or its phenotypes in the TLGS population (20).

Considering RFs of incidence of type 2 diabetes (T2DM), Cox proportional hazard model showed that neither SBP nor DBP were associated with incident DM in the total population or in either gender separately (21). A principal component analysis regarding the effects of components of metabolic syndrome on the incident T2DM over 10 years of F/U (22), conducted on 1861 men and 2706 women aged 20 - 60 years, identified BP as one of three contributing RFs for the incidence of T2DM, which was 7.14% and 7.57% in men and women, respectively. Multivariate ORs (95% CI) of incident T2DM for the third versus the first tertile of BP were 2.23 (1.31 - 3.78) and 2.13 (1.34 - 3.40) in men and women, respectively. Regarding dichotomized definitions, high BP ($\geq$ 130/85 mmHg) also had multivariate ORs (95% CI) of 1.47 (1.11 - 1.96) and 1.36 (1.02 - 1.81) for incident T2DM in men and women, respectively.

To investigate the impact of different combinations of glucose tolerance and BP status on the development of T2DM, 8231 individuals without diabetes at baseline were recruited (23). During a median follow-up of > 10 years, the overall incidence rate for T2DM was 12.2 per 1000 person-years. Compared to normal glucose tolerance/normal BP (NGT/NBP) as reference, multivariate adjusted HRs (95% CI) for incident T2DM were 1.34 (1.06 - 1.69), 6.44 (5.17 - 8.01), 7.22 (5.71 - 9.12) and 1.65 (1.26 - 2.17) for NGT/PreHTN, PreDM/PreHTN, PreDM/HTN and NGT/HTN, respectively. Results of the sensitivity analysis with multiple imputed baseline missing data and inverse probability weighting in the Cox regression analysis were approximately the same as the primary analyses.

3.8. Blood Pressure, Cardiovascular Disease and Mortality

Table 2 represents data regarding the associations of BP components as continuous variables (24) and different HTN phenotypes (25) with CVD and mortality in the middle-aged and older TLGS population, followed-up until March 2009. During a median F/U of 8.7 years in 5991 subjects, aged $\geq$ 30 years without baseline CVD or use of antihypertensive medication (24), after multivariate adjustment, except for DBP and mean arterial pressure [MAP: 1/3 (SBP + 2 $\times$ DBP)] with regard to all-cause mortality in individuals, aged $\geq$ 60 years, all BP components were predictive of CVD events and total mortality in middle-aged and elderly individuals. The discriminatory powers of all BP measures in multivariate models for CVD events and all-cause mortality, calculated by the C index, generally declined with increasing age. Regarding the fitness and discrimination of models, DBP, pulse pressure (PP: the difference between SBP and DBP) and MAP were not superior to SBP, supporting SBP predictability for CVD events and all-cause mortality, compared with other BP measures (24).

During > 10 years F/U of 6974 participants aged 30 to < 65 years and 882 participants aged $\geq$ 65 years, 490 and 194 CVD events also 152 and 183 deaths occurred, respectively (25). In both middle-aged and elderly populations, ISH, systolic-diastolic HTN (SDH), and uncontrolled BP (UBP) increased CVD risk. Regarding mortality, findings revealed significant discrepancies; for all-cause mortality in the middle-aged group, IDH and UBP were significant predictors, whereas in the elderly group, IDH, SDH, and

Table 2. Multivariate-Adjusted Cox Proportional Hazard Ratios (95% CI) of a 1SD Increase in Each BP Components and HTN Phenotypes for Incident CVD and Mortality Outcomes in the Middle-Aged and Elderly Population[a,b,c]

	CVD	All-Cause Mortality	CVD Mortality
Middle-aged			
SBP	1.43 (1.26 - 1.61)	1.67 (1.35 - 2.06)	NA
DBP	1.24 (1.08 - 1.42)	1.47 (1.11 - 1.94)	NA
PP	1.39 (1.23 - 1.57)	1.55 (1.24 - 1.93)	NA
MAP	1.37 (1.20 - 1.56)	1.62 (1.24 - 2.10)	NA
ISH	1.52 (1.08 - 2.14)	1.03 (0.50 - 2.09)	0.96 (0.33 - 2.79)
IDH	1.31 (0.90 - 1.91)	2.01 (1.11 - 3.65)	1.26 (0.38 - 4.15)
SDH	1.52 (1.12 - 2.05)	1.62 (0.95 - 2.75)	1.70 (0.76 - 3.80)
CBP	1.36 (0.85 - 2.18)	1.10 (0.43 - 2.78)	1.17 (0.27 - 5.06)
UBP	3.09 (2.31 - 4.14)	2.95 (1.78 - 4.88)	5.67 (2.93 - 11.00)
Elderly			
SBP	1.38 (1.18 - 1.63)	1.28 (1.04 - 1.56)	NA
DBP	1.20 (1.00 - 1.44)	1.05 (0.85 - 1.28)	NA
PP	1.29 (1.10 - 1.51)	1.29 (1.07 - 1.56)	NA
MAP	1.33 (1.11 - 1.60)	1.17 (0.95 - 1.44)	NA
ISH	1.97 (1.33 - 2.91)	1.45 (0.96 - 2.18)	2.24 (1.19 - 4.21)
IDH	1.65 (0.66 - 4.13)	3.23 (1.46 - 7.16)	3.80 (1.11 - 13.02)
SDH	1.89 (1.20 - 2.98)	2.01 (1.26 - 3.20)	3.20 (1.60 - 6.42)
CBP	1.14 (0.59 - 2.19)	1.87 (1.04 - 3.37)	2.86 (1.21 - 6.76)
UBP	1.81 (1.17 - 2.80)	1.15 (0.70 - 1.87)	1.44 (0.65 - 3.17)

Abbreviations: CBP, controlled BP (DBP < 90 and SBP < 140 and antihypertensive drug consumption); CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HTN, hypertension; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation; SDH, systolic diastolic hypertension; UBP, uncontrolled BP (DBP at least 90 or SBP at least 140 and antihypertensive drug consumption).

[a] Age cutoffs for definition of middle-aged and elderly population were 60 and 65 years in the studies related to BP components (13) and HTN phenotypes (14), respectively.

[b] Considering BP components (SBP, DBP, PP, MAP), covariates included in the multivariate model were sex, smoking status, family history of premature CVD, diabetes, lifestyle intervention group, body mass index (BMI), waist circumference and cholesterol for CVD events and sex, BMI, diabetes and smoking status for all-cause mortality.

[c] For HTN phenotypes (ISH, IDH, SDH, CBP, UBP), covariates included in the multivariate model were age, sex, smoking status, diabetes status, hypercholesterolemia, low HDL, and BMI. Reference group was no HTN defined as SBP < 140 mmHg and DBP < 90 mmHg.

controlled BP (CBP) increased the risk. In middle-aged participants, only UBP was associated with incident CVD mortality and was the sole phenotype that was not an independent predictor of CVD death in the elderly. The notable finding of this study was the increased mortality risk in elderly patients with CBP (25).

Considering age-stratified analyses, the independent risk of CVD according to BP categories during 9.3 years of F/U, was assessed among 5064 middle-aged (30 to < 60 years) and 1209 elderly (≥ 60 years) participants of TLGS with no baseline CVD (26). Both high normal BP (SBP 130 - 139 mmHg or DBP 85 - 89 mmHg) and HTN were associated with incident CVD in the middle-aged participants [multivariate HRs (95% CI, P value): 1.62 (1.11 - 2.37, 0.013) and 2.20 (1.57 - 3.09, < 0.001), respectively]; however, in the eldely, high normal BP was not a CVD risk factor [HR (95% CI): 0.89 (0.51 - 1.54)], while HTN was associated with a HR (95% CI) of 2.09 (1.36 - 3.21) for CVD.

Parizadeh et al. investigated the association of changes in BP components between baseline examination (1999 - 2001) of the TLGS and the second examination (2002 - 2005) with incident CVD up to March 2012 (27). During a median F/U of 6 years after the second visit, 303 CVD events occurred among 3569 individuals. Each 1 SD increase in SBP, DBP and MAP was significantly associated with 21%, 22%, and 95% increased CVD risk after adjustments for baseline value of each BP component, SBP/DBP/PP/MAP change, and several other covariates (27).

During 9.3 years of F/U of 2548 participants without a history of CVD, aged ≥ 50 years, high BP as a component of the metabolic syndrome (MetS) was found to be associated with the incident CHD after adjustment for all MetS components (28); corresponding HRs (95% CI, P value) were 1.89 (1.42 - 2.51, < 0.001), 1.87 (1.44 - 2.43, < 0.001) and 1.89 (1.49 - 2.41, < 0.001), based on JIS, IDF and WHO definitions of MetS, respectively.

Two studies from the TLGS investigated HRs and population attributable fraction (PAF) of risk factors of CHD or CVD (29, 30); in 2889 men and 3803 women, aged 30 - 74 years, with no history of CVD at baseline, 11.9 and 6.5 CHD events per 1000 person-years occurred in men and women, respectively, during a median F/U duration of 10.3 years. HRs (95% CI) of HTN (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or taking HTN medication) for incident CHD were 1.8 (1.4 - 2.2) and 2.1 (1.6 - 2.8) in men and women, respectively. Average hypertension-related PAFs for CHD were 9.4 and 17.0% in men and women, respectively (29). With extension of F/U duration up to 2012, among 8108 participants without prevalent CVD, 827 first CVD events, including stroke, and 551 deaths occurred. Using multivariate Cox proportional hazard models with obesity mediators (DM, HTN, lipid profile and CKD), preHTN was not determined as a potential CVD or all-cause mortality RF; however, HTN had HRs (95% CI, P value) of 1.79 (1.46 - 2.19, < 0.0001) and 1.43 (1.11 - 1.84, 0.005) for CVD and all-cause mortality, respectively. Corresponding PAFs (95% CI) were 21.62% (14.49 - 28.79) and 17.13% (5.25 - 27.84) for CVD and all-cause mortality events, respectively (30).

In a recently-published article from the TLGS (31), sex-specific incidence rates and RFs of premature CVD, defined

as having a CVD event before the age of 55 and 65 years in men and women, respectively, have been investigated during a median period of 11.74 years. Reported HRs (95% CI, P value) and PAFs (95% CI) related to HTN were 1.65 (0.97 - 2.81, 0.06) and 8.7% (-0.5% -19.3%) in men and 1.54 (1.01 - 2.34, 0.04) and 16.8% (0.4% - 32.1%) in women. PreHTN was not recognized as a significant RF for premature CVD, either in men or in women.

Finally, results of a Cox proportional hazard model evaluating the effect of different combinations of BP and glucose tolerance status on CVD and all-cause mortality in 7619 participants, aged $\geq$ 30 years (32) reported that in a median F/U of 11.3 years, 696 CVD and 412 all-cause mortality events occurred in these participants with no baseline CVD. Based on the calculated multivariate HRs, all hypertensive phenotypes were significantly associated with CVD, CHD and mortality events, with the highest risk in participants with both HTN and DM. Moreover, preHTN and DM phenotype increased CVD risk by 71%. These findings underscore the importance of HTN with regard to CVD and mortality, regardless of glucose tolerance status (32).

3.9. Blood Pressure and Stroke

When looking at the findings of studies from TLGS related to BP and stroke in this section, it should be taken into account that in all of the above-mentioned studies about CVD events, stroke was included as one of the CVD outcomes. Here, we present data available on cerebrovascular events as a separate outcome.

In a study aimed at determining RFs for stroke, 1089 men and 1289 women aged $\geq$ 50 years were followed for 9.3 years (33). All cases of definite or possible stroke or transient ischemic attack (TIA) were included in the cerebrovascular accident (CVA/stroke) definition. For 69 CVA events, multivariate Cox proportional HR (95% CI, P value) and PAF related to HTN were 3.03 (1.76 - 5.22, < 0.001) and 48.6%, respectively. Cox analysis considering continuous variables revealed that each mmHg increase in SBP and DBP was associated with 13% and 55% increased risk of stroke, respectively. Similar results were reported for ischemic stroke (IS). Overall, among different modifiable and non-modifiable RFs, HTN showed the greatest PAF for stroke events.

During 9.3 years of F/U of 2548 participants, aged $\geq$ 50 years, without a history of CVD, high BP as a component of the metabolic syndrome (MetS) was associated with incident CVA after adjustment for all MetS components. Corresponding HRs (95% CI, P value) were 3.05 (1.46 - 6.34, 0.003), 3.48 (1.72 - 7.02, < 0.001) and 2.87 (1.63 - 5.06, < 0.001) based on JIS, IDF and WHO definitions of MetS, respectively (28).

Recently, a sophisticated survival tree model was used to explore interactions between risk factors of IS in 3088 TLGS participants, aged $\geq$ 50 years with 106 IS events during 12 years of F/U (34). Multivariate Cox proportional hazard model documented DBP as one of the RFs [1.04 (1.02 - 1.05)]. Based on the survival tree analysis, DBP was the most important predictor of IS not only in the middle aged but also in the elderly, such that the highest risk among both age groups was attributed to DBP $\geq$ 97 mmHg and DBP $\geq$ 100 mmHg, respectively. Overall, the highest and lowest risks identified by the survival tree were related to subjects $\geq$ 60.5 years with DBP $\geq$ 100 mmHg and subjects < 60.5 years with DBP < 97 mmHg, respectively (34).

3.10. Studies on BP in the Elderly as a Special Population

In addition to above-mentioned data regarding different aspects of BP and HTN in older adults of the TLGS as an age subgroup, there are a few studies considering the elderly as the only study population.

Mohebi et al. investigated CVD and mortality risk in 1845 participants, aged $\geq$ 60 years, free of baseline CVD, according to different BP categories (35). During a median F/U of 10 years, 380 CVD and 260 mortality events occurred. Cox proportional hazard regression was used with adjustment for age, sex, TC, HDL-C, current smoking, fasting plasma glucose, BMI, and WC. Compared to the reference group (those with SBP < 120 mmHg and DBP < 80 mmHg), individuals with 140 mmHg < SBP < 150 mmHg and DBP < 90 mmHg [HR (95% CI, P value): 1.79 (1.17 - 2.74), 0.007] and those with SBP $\geq$ 150 mmHg and/or DBP $\geq$ 90 mmHg mmHg [HR (95% CI, P value): 1.73 (1.24 - 2.42), 0.001] showed increased risk of CVD events (35). These findings emphasize the importance of SBP levels of 140 - 150 mmHg in the elderly population with regard to CVD outcomes.

To investigate the relationship between different anthropometric measures and their mediating factors with CVD and mortality in the elderly, 881 TLGS participants, aged $\geq$ 65 years and free of CVD at baseline were selected (36). During a median F/U of 9.5 years, 193 CVD events and 183 deaths occurred. The confounder- and mediator-adjusted Cox proportional hazard analysis showed that only central adiposity measures were associated with a significantly increased risk of CVD/CHD and among all of the mediators including hypercholesterolemia, DM and HTN, HTN had the most impact, accounting for 30% - 45% of the excess risk of central adiposity measures for CVD events.

3.11. BP and Chronic Kidney Disease

Based on the Tohidi et al. study regarding the incidence and RFs of CKD (eGFR < 60 mL/min/1.73 m^2) in the TLGS population during a mean F/U of 9.9 years, high normal BP and

HTN were determined as significant RFs for incident CKD, only in men; corresponding ORs (95% CI, P value) were 1.74 (0.99 - 3.04, 0.05) and 2.20 (1.38 - 3.52, 0.001), respectively (36).

4. Conclusions

According to data regarding the prevalence and incidence of preHTN and HTN reported in the aforementioned studies and their contribution to cardiovascular morbidity and mortality in the TLGS population as a representative sample of Tehranian population, it is recommended that interventions be prioritized for lifestyle modifications for the prevention and appropriate management of preHTN/HTN.

Moreover, further studies considering the associations between BP in adolescents and the long term incidence of hard outcomes as well as randomized controlled trials on the effects of control of modifiable risk factors of HTN and proper management and monitoring of BP are warranted.

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Footnote

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Metabolic Syndrome: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: In recent decades, investigations have been focused on the definition, incidence and predictors of metabolic syndrome (MetS) in Iranians. This study aimed to review systematically investigations on MetS, conducted among the Tehran lipid and glucose study (TLGS) participants.

Evidence Acquisition: Literature on MetS documented by TLGS studies published from 2000 to 2017 were searched using Pubmed and Scopus database in English language with a combination of following keywords: Metabolic syndrome, TLGS.

Results: The harmonized definition of MetS was confirmed, based on the estimated cut point of waist circumference (WC) $\geq$ 95 cm for both genders in Iran. The incidence rate was 550.9/10000 person/years, lower among women (433.5/10000) than men (749.2/10000). The prevalence of abdominal obesity, high triglycerides (TG), low high density lipoprotein cholesterol (HDL-C), high blood pressure (BP), and high fasting blood glucose (FBG) was 30, 46, 69, 34, and 12%, respectively. The prevalence of MetS in adolescents was 10.1% with no significant difference between boys and girls (10.3% in boys and 9.9% in girls). A strong association of WC (OR: 2.32, CI: 2.06 - 2.59) and TGs (OR: 1.95, CI: 1.65 - 2.11) with development of MetS was found. In adolescent boys, WC had the highest OR for MetS risk. WHO-defined MetS was a significant predictor of total and cardiovascular mortality both in men (HR: 1.66, CI: 1.23 - 2.24; HR:1.93, CI: 1.26 - 2.94) and women (HR: 2.01, CI: 1.39 - 2.88; HR:2.71, CI: 1.44 - 5.09).

Conclusions: Our results indicate high incidence of MetS in Tehranian adults and adolescents; high WC also appears to be a strong predictor of MetS. All definitions of MetS predicted cardiovascular disease.

Keywords: Metabolic Syndrome, Obesity, Hypertension, Hyperlipidemia, HDL-C, LDL-C, Tehran Lipid and Glucose Study

1. Context

Metabolic syndrome (MetS) is characterized as having 3 or more risk factors including abdominal obesity, hypertension, hyperglycemia, and dyslipidemia, is a pathological condition which increases risk of various non-communicable diseases (NCDs) (1). There is limited global data for prevalence of MetS but over a billion people around the world were estimated to have MetS. Its prevalence varies worldwide and it is highly associated with urbanization and life style (2). A nationally representative study of Iranians living in both urban and rural area of 30 provinces of Iran, aged 25 - 64 years, showed a high prevalence for MetS in 2007 (3). In 1999 - 2001, it has been estimated that 30.1% adults living in Tehran have MetS (4). In addition to the variation in prevalence, the predictors of MetS also differ across populations (5).

The rate of MetS is also high among overweight/obese children and adolescent, and is simultaneously increasing with the prevalence of obesity. At least one criteria of MetS can be seen in 90% of obese children and adolescent (6). MetS in childhood is associated with higher risk of diabetes and coronary heart diseases in adulthood (7).

Tehran lipid and glucose study (TLGS) is an ongoing study started in 1999 with a representative sample of 15005 individuals aged $\geq$ 3 years, recruited from residence of district no.13 of Tehran, the capital of Iran (8). This prospective study provides an opportunity to study different aspects of NCDs in this Middle-Eastern population. This study aimed to review all findings of studies conducted in framework of TLGS regarding the prevalence and incidence of MetS and its predictors in different age groups, providing a deeper

insight into this syndrome in this population in order to design better preventive strategies for high risk individuals.

2. Evidence Acquisition

2.1. Methods

All English-language studies focused on the prevalence and incidence of MetS, and its potential predictors in different age groups in the framework of the TLGS, were searched using PubMed, Scopus, and Embase databases. A structured search strategy with using combination of keywords "metabolic syndrome AND Tehran lipid and glucose study" was conducted to identify records in each database. Eventually, 35 relevant papers were included in this review. Seven papers described different definition of MetS in the TLGS population; its prevalence and incidence were described in 10 papers. Prevalence, incidence and risk factors of MetS in children and adolescents were clarified in 8 articles. Ten studies focused on the potential usefulness of MetS in prediction of cardiovascular (CVD) events, all-cause and CVD mortality and type 2 diabetes in different age groups.

2.2. Metabolic Syndrome Definitions

MetS is a complex accumulation of risk factors containing hypertension, central obesity, high fasting blood glucose (FBG) and dyslipidemia. The World Health Organization (WHO), Adult Treatment Panel (ATP) III, International Diabetes Federation (IDF), American Heart Association (AHA), and the National Health Lung and Blood Institute (NHLBI) have presented various definitions for MetS (Table 1). Considering the sharp rising trend in the prevalence of obesity and MetS in Iran, having a uniform and harmonized definition for waist circumference (WC) and MetS would facilitate the comparison of clinical and epidemiological investigations for trend studies; the Iranian national committee of obesity hence designated a cut point of WC $\geq$ 95 cm for both genders in Iranian adults (9).

3. Results

3.1. Prevalence and Incidence of Metabolic Syndrome in Adults

The prevalence of MetS in a study population of 10368 adults (4397 men and 5971 women), aged $\geq$ 20 years recruited at the initiation of TLGS (1999 - 2001), was 30.1% and age-standardized prevalence was 33.7% based on the ATP III definition; the prevalence was higher in women (42%) than in men (24%), and increased with aging in both genders. The most prevalent metabolic abnormality was low-HDL, followed by high TG, hypertension, abdominal obesity, and high FPG (4). Another study conducted on 10368 adults, aged $\geq$ 20 years suggested a prevalence ranging between 17.5 - 31.7%, depending different definition for MetS; highest and lowest estimations was based on the ATP III and the WHO definitions, respectively (10). The prevalence of MetS in elderly participants, aged $\geq$ 65 years, ranged between 42 and 52.5% based on different definitions. High BP was the most prevalent component based on the ATP and the IDF definitions, whereas obesity was the most prevalent, based on the WHO definition. The prevalence of MetS in the elderly was lower in men than in women (11).

Another study conducted among 1737 men and 1707 women with normal weight (BMI = 18.5 - 24.5) also reported high prevalences of 9.9% in men and 11% in women based on the ATP III definition (12). The prevalence of MetS rose 4-fold during 6.6 years in a normal weight adult population from 2.3% at initiation of the TLGS study to 9.6% in the third examination (2005 - 2008), an incremental trend significant only among men accompanied by an increasing trend in abdominal obesity, seen only in men (13).

The age-adjusted incident rate of MetS during a 3-year follow-up was estimated to be 20.4 (95% CI: 19.6 - 21.2) in 2217 Iranian participants, aged $\geq$ 20 years (14). The incidence rate of MetS during 9.3 years of follow-up was 550.9/10000 person/years, and risk of developing MetS was 50% lower in women, compared with men (749.2/10000 person/years in men and 433.5/10000 person/years in women) based on the Joint Interim Statement (JIS) definition (15).

The prevalence of MetS is high among Tehranian populations in all adult age groups, and is even higher among normal weight adults, and the increasing trend in prevalence of MetS and abdominal obesity especially, especially among men with normal weight, should be considered in future public health programs. The incidence of MetS was higher among men which may be due to the rising trend of abdominal obesity observed more among men than women.

Nationally representative study of prevalence of MetS also showed a high burden for MetS with age-adjusted prevalence of 34.7 % (95% CI = 33.1 - 36.2%) based on the ATP III definition in 2007 on 3024 living in 30 provinces of Iran. Consistent with our findings, the prevalence reported for women in this study was higher than in men, and an increase in prevalence of MetS was observed by increasing age in both sexes. Low-HDL was the most prevalent of metabolic abnormalities as was seen in TLGS (3) (Table 2).

3.2. Predictors of Metabolic Syndrome

A 6.5-year cohort study on subjects aged 20 - 87 years aimed to resolve which constituent of the MetS is the best predictor of its progress; WC, HDL-C and TG predicted the development of MetS better than blood pressure (BP) or FBG; a model that comprised WC and TG or WC and HDL-C

Table 1. Important Definitions of Metabolic Syndrome in Adults

	IDF	ATP III	EGIR	WHO
Definitions	Abdominal obesity + two or more of these components	Presence of three or more of these components	Elevated plasma insulin (> 75th percentile) plus two other factors from among the following:	Glucose intolerance, impaired glucose tolerance (IGT) or diabetes mellitus (DM), and/or insulin resistance, together with two or more of the components listed below:
BMI, kg/m^2	BMI is > 30	-		Body mass index (BMI) > 30
WHR or WC, cm	Dependent to population If BMI is > 30kg/m^2, central obesity can be assumed and waist circumference does not need to be measured	Dependent to population	Waist circumference (WC) $\geq$ 94 cm in men and $\geq$ 80 cm in women	Waist/hip ratio (WHR) > 0.9 in men and > 0.85 in women
TG, mg/dL	$\geq$ 150 (1.7 mmol/L) or specific treatment for this lipid abnormality	> 150 or drug treatment for elevated triglycerides	$\geq$ 150	$\geq$ 150
HDL, mg/dL	< 40 (1.03 mmol/L) in males < 50 (1.29 mmol/L) in females or specific treatment for this lipid abnormality	Men: < 40 Women: < 50	< 39 for both men and women	< 35 in men and < 39 in women
BP, mm Hg	Systolic BP $\geq$ 130 or diastolic BP $\geq$ 85 or treatment of previously diagnosed hypertension	> 130/85 or drug treatment for elevated blood pressure	$\geq$ 140/90 or on antihypertensive treatment	$\geq$ 140/90
FBG, mg/dL	(FPG) $\geq$ 100 (5.6 mmol/L), or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100, OGTT is strongly recommended but is not necessary to define presence of the syndrome	> 100 or drug treatment for elevated glucose	Impaired fasting glucose (IFG) or IGT, but no diabetes	
Albuminuria, μg/min	-		-	Urinary albumin excretion rate $\geq$ 20 μg/minute or albumin/creatinine ratio $\geq$ 30 μg/mg.

Abbreviations: AACE, American Association of Clinical Endocrinologists; AHA,/NHLBI, American Heart Association/National Heart, Lung and Blood Institute; BMI, body mass index; BP, blood pressure; EGIR, Europeran Group for Study of Insulin Resistance; FBG, fasting blood glucose; HDL, high density lipoprotein-cholesterol; IDF, International Diabetes Federation; INCO, Iranians National Committee of Obesity; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; TG, triglyceride; WC, waist circumference; WHO, World Health Organization; WHR, waist to hip ratio.

predicted MetS, like a model that constituted all five MetS components (19).

A 6.6 year-cohort study investigating the effect of changes in WC on MetS status and its parameters in adults concluded that waist gain, although mild, was a risk factor of the development of MetS and its components (20). During a three year follow-up, weight gain > 1.3% initial weight in women and > 4% in men were related to increased risk of MetS (14). A population-based cohort study confirmed the importance of BP, WC and lipid measurements in risk stratification of MetS in adulthood (21).

These findings are in agreement with previous study conducted among Iranian populations (22). Obesity, especially central obesity, increased risk of developing MetS 19-fold among 15 - 65 years participants (23), which could be due to WC being strongly associated with chronic systemic low-grade inflammation (24), which is considered to be the underlying cause of MetS (25), indicating that greater decreases in WC with medical weight loss are related to significant improvement in components of MetS, independent of sex (26).

The independent predictors of MetS include all components of MetS, obesity, family history of diabetes and age. Moreover individuals in the 4th quartile of HOMA-IR had significant risk for MetS in both genders (15). The independent association of family history of diabetes with MetS indicates that genetic susceptibility plays a role in the risk of MetS (27).

The incidence of MetS among 433 healthy obese individuals was 44.0% (36.8 - 55.0) over 10 years of follow-up; predictors of MetS in healthy obese subjects included hypertension, high TG, low HDL-C and insulin resistance; WC was also a weak predictor of MetS in these subjects (5). In spite of short-term follow-up studies reporting no relation between metabolically healthy obesity and cardiovascular disease, long-term follow-up studies showed an increased

Table 2. Prevalence and Incidence of Metabolic Syndrome in the Tehran Lipid and Glucose Study

Year	Reference No.	Number of Participants	Age, y	BMI Group, kg/m^2	Criteria of Diagnosis	Prevalence, %	Incidence, %	Incidence Rate
1999 - 2001	(4)	10368	≥ 20	-	ATP	33.7	-	-
1999 - 2001	(10)	10368	≥ 20	-	ATP	32.1	-	-
1999 - 2001	(10)	10368	≥ 20	-	IDF	33.2	-	-
1999 - 2001	(10)	10368	≥ 20	-	WHO	18.4	-	-
1999 - 2001	(11)	720	≥ 65	-	ATP	50.8	-	-
1999 - 2001	(11)	720	≥ 65	-	IDF	41.9	-	-
1999 - 2001	(11)	720	≥ 65	-	WHO	41.8	-	-
1999 - 2001	(12)	3444	≥ 20	18.5-24.9	ATP	9.9 (men) 11 (women)	-	-
1999 - 2001	(13)	5269	≥ 20	18.5-24.9	IDF	2.3	-	-
2002 - 2005	(13)	5269	≥ 20	18.5-24.9	IDF	4.0		
2005 - 2008	(13)	5269	≥ 20	18.5-24.9	IDF	9.6	-	-
From 1999 - 2001 to 2002 - 2005	(14)	2217	≥ 20	> 18.5	ATP	-	20.4	-
From 1999 - 2001 to 2008 - 2011	(15)	2858	≥ 20	-	JIS	-	-	550.9/10000
1999 - 2001	(16)	3036	10 - 19	-	ATP	10.1	-	-
From 1999 - 2001 to 2003 - 2005	(17)	932	10 - 19	-	ATP	-	5.2	-
From 1999 - 2001 to 2003 - 2005	(17)	932	10 - 19	-	IDF	-	6.8	-
From 1999 - 2001 to 2003 - 2005	(17)	932	10 - 19	-	AHA	-	8.3	-
From 1999 - 2001 to 2003 - 2005	(17)	932	10 - 19	-	NHANES	-	8.8	-
1999 - 2001	(18)	1424	11 - 18	-	Cook	13.1	-	
1999 - 2001	(18)	1424	11 - 18	-	de Ferranti	26.4	-	
1999 - 2001	(18)	1424	11 - 18	-	Pediatric NCEP	11.7	-	
1999 - 2001	(18)	1424	11 - 18	-	Pediatric IDF	8.4	-	

Abbreviations: AHA: American Heart Association; ATP III: adult treatment panel III; IDF: International Diabetes Federation; JIS: joint interim statement; NHANES: National Health and Nutrition Examination Survey; WHO: World Health Organization.

risk, since metabolic abnormalities occurred over longer follow-up periods (28).

A cross sectional study conducted on 5720 women and 4040 men, reported that hip circumference is independently and inversely associated with high LDL-C, diabetes, hypertension, low HDL-C and abnormal glucose homeostasis (29, 30). This finding confirms the importance of hip circumference measurements in epidemiological studies which are in line with previous studies in Australian (31) and Canadian (32) populations. It seems this association is independent of race.

3.3. Metabolic Syndrome Studies in Children and Adolescents

Although MetS has been extensively studied in adults (33), limited attention has been focused on children and adolescents. To investigate the prevalence of MetS in Iranian adolescents based on the ATP definition, a cross-sectional study (1999 - 2001) was conducted among adolescents, aged 10 - 19 years. The prevalence of MetS was 10.1% with no significant difference between boys and girls (10.3% in boys and 9.9% in girls), although those with a family history of diabetes and overweight had higher prevalence of MetS. Odds of MetS was higher in girls than boys [1.34 (1.03 -

1.76)] and in overweight than normal weight ones [17.8 (13.2 - 24)]. Of MetS components, low HDL-C (42.8%) and high TGs (37.5%) were the most prevalent, and high FBS (0.6%) was the least prevalent component (16). The incidence of MetS between the 1999 - 2001 and 2003 - 2005 surveys was 5.2% (95% CI: 3 - 6) based on ATPIII, 6.8% (95% CI: 5 - 8) based on IDF, 8.3% (95% CI: 6 - 10) based on AHA, and 8.8% (95% CI: 6 - 10) based on NHANES definitions (17). Furthermore, based on different definitions, the prevalence of MetS according to the Cook, de Ferranti, pediatric ATPIII and pediatric IDF was 13.1, 26.4, 11.7, and 8.4, respectively. Findings showed that the pubertal group (11 - 14 years) had higher prevalent MetS than those in late-pubertal groups (15 - 18 years). Most frequent MetS constituents found in two groups were low HDL-C and high TGs (18). The prevalence and incidence of MetS among adolescents of TLGS are comparable to those of other study in Iran (34). According to a 2013 systematic review, median prevalence were 5.2% in boys and 3.1% in girls (35). It seems that prevalence of MetS among adolescents varies by different study years with recent studies indicating a decreasing trend of MetS; however, studies periods in TLGS were 1991 - 2005 and no other study has reported recent trends of MetS data from the TLGS. Observations from two systematic reviews prior to 2013 suggest increasing prevalence of the MetS in youth, particularly in regions, such as the Far East and the Indian Subcontinent indicate that potential gender and regional differences in prevalence and that it may prove difficult to estimate the likely prevalence of MetS. More data is also needed to the two components of high TGs and low HDL-C which are determining factors of MetS worldwide (36, 37).

Another important explanation for the varying prevalence of MetS between TLGS and other studies is the use of different definitions. There is no general concern on the cut-off rates and its parameters (38). Different definitions of MetS in adolescents including Cook, Duncan, Boney, Cruz, and de Ferranti, showed that the highest correlation and prediction of adult MetS after 6.6 years of follow-up, using ATPIII criteria, was attained by de Ferranti's definition (39). Furthermore, in a longer follow-up study of 10.4 years with the joint interim statement (JIS) definition for adult MetS, the accordance of childhood MetS definitions and JIS was weak (κ = 0.094 - 0.255); however, the best accordance was found between JIS and Cook's definition in the late-pubertal group (κ = 0.255), in which group, the predictive power of each childhood definition was slightly higher for adulthood MetS. Among the Cook, de Ferranti, pediatric ATPIII and pediatric IDF definitions, Cook's and deFerranti's had better predictive powers (18). Besides the classic definition of MetS as having three of the five components including central obesity, hypertension, high fasting blood glucose, low HDL-C, and high TGs, factor analysis has been used to identify cardio-metabolic risk factor models in adolescents. Using exploratory factor analysis to extract factor structure of MetS components, six measured variables were reduced to two sets of inter-correlated factors, BP and adiposity/lipids. The goodness of fit of the two-factor model was appropriate for boys and girls (40).

Except the MetS entity in adolescents, different metabolic phenotypes have recently been investigated in this age group. Adolescents with the hypertriglyceridemic waist (HW) phenotype had higher prevalence of all metabolic risk factors including high LDL-C, low HDL-C, and hypercholesterolemia than did those without this phenotype (41).

Prospective studies have reported that risk factors cluster together from childhood into adulthood and are strongly associated with obesity and insulin resistance. To find out the predictive value of WC and BMI, their best cut-off points for the incidence of MetS, a 6.6 year, follow up study was conducted on children; conclusions convey that both BMI and WC have the same power to predict MetS, therefore, children with higher BMI or WC are more exposed to MetS (42). However, when adolescents were followed to explore the best anthropometric parameter to predict early adulthood MetS, in boys, WC had the highest OR for the MetS risk, followed by waist-to-height ratio (WHtR). Adjusting BMI in addition to WC did not change the results in the 11 - 14-year age group, suggesting that WC may predict MetS risk above BMI. None of the anthropometric parameters were observed to have significant relationships with subsequent MetS risk in girls (43). In addition to anthropometric indices, several metabolic factors including high TGs/low HDL-C, high TG/high WC, high WC/low HDL, and high BP/low HDL-C phenotypes in adolescents predicted early adult MetS, independent of baseline BMI Z-Score and BMI change (44). An important finding was that adolescent MetS or higher weight gain were not able to predict early adult MetS, after controlling for adult BMI. In addition, the risk of developing MetS in early adulthood was higher among participants who were constantly obese or who became obese in adulthood than those who were overweight or obese during adolescence but non-obese in adulthood (45) (Table 2).

3.4. MetS Prediction for CVD and Diabetes

In a study conducted on 7932 subjects, aged $\geq$ 30 years who were followed for 9.0 $\pm$ 2.3 years, WHO-defined MetS was a significant predictor of total and cardiovascular mortality in men (HR=1.66, 95% CI=1.23 - 2.24, and HR=1.93, 95% CI = 1.26 - 2.94) and women (HR = 2.01, 95% CI = 1.39 - 2.88 and HR = 2.71, 95% CI = 1.44 - 5.09) (46). WHO-defined MetS could also predict 10-year risk of CVD and all-cause mortality events (HR=1.55, 95% CI=1.15 - 2.09, and HR=2.08 95% CI =1.23 - 3.51, respectively) in 922 adults, aged $\geq$ 65 years (47); JIS-defined MetS showed a risk for CVD mortality (HR=1.65

(95% CI = 1.03 - 2.65) (47). In a 9.3 year follow-up of 5198 non-diabetic individuals, aged ≥ 30 years (mean age 45.6 years, 45% men), the HRs of CVD events according to the NCEP-ATP III, AHA/NHLBI, IDF and JIS definitions of MetS were 1.55 (1.21 - 2.00), 1.73 (1.35 - 2.20), 1.54 (1.22 - 1.94) and 1.70 (1.34 - 2.17), respectively (48). Evaluation of agreement between different definitions of MetS and insulin resistance in 347 non-diabetic individuals (aged ≥ 20 years) also showed poor agreement between ATP III or JIS and HOMA-IR (Kappa = 0.14 and 0.16, respectively); both criteria had also low sensitivities and specificities for detecting insulin resistance (49). Moreover, findings of a principal component analysis, of data of a 10-year follow-up performed to extract standardized factors from MetS components, identified three factors including BP, lipids and glycemia; WC was shared in three all factors (50); their results showed that BP, lipids and glycemia were related to the incidence of diabetes (OR = 2.23, 95% CI = 1.31 - 3.78, OR = 1.89, 95% CI = 1.27 - 3.67, and OR = 7.54, 95% CI = 4.09 - 13.91, respectively), in men and (OR = 2.13, 95% CI = 1.34 - 3.40, OR = 2.06, 95% CI = 1.35 - 3.15, and OR = 13.91, 95% CI = 7.29 - 26.51, respectively), in women, for the third versus the first tertile of these standardized factors (50).

All definitions of MetS were associated with cardiovascular disease (CVD). In a cross-sectional study, all definitions of MetS were related to CHD after adjustment for controlling factors in both genders (51). During 9.3 years of follow-up, the hazard ratios (HR) of MetS defined by JIS were 2.71 (1.57 - 4.68) and 2.07 (1.63 - 2.64) respectively for incident cardiovascular events and CHD; However, after controlling for MetS components, these relationship were no longer significant. In all definitions, high BP predicted both CVD and CHD events, and high FBS was also an independent predictor for CHD (52, 53). In subjects with diabetes, adding MetS did not change the CVD risk compared to individuals without MetS; however, the risk of CVD in IFG/IGT subjects increased 2.5 fold after addition of MetS, compared to IFG/IGT individuals without MetS (54).

Moreover, although all definitions of MetS seem to be predict type 2 diabetes, IGT had the highest predictive power for diabetes, compared to other definitions (55).

Previous studies confirmed the potential role and clinical usefulness of MetS for predicting CVD events and type 2 diabetes. A 18-year follow-up of Finnish males and females indicated that subjects with MetS had a 2.01-fold (95% CI = 1.46 - 2.77) higher risk for cardiovascular events, compared with subjects without MetS; compared with those without any components of MetS, having five components of MetS was related to hazards of 7.89 (2.26 - 27.60) for cardiovascular events (56). Having MetS was also related to incident diabetes, regardless of whether the MetS was defined according to NCEP ATPIII (OR = 2.03, 95% CI = 1.10 - 3.75) or the IDF criteria (OR = 2.14, 95% CI = 1.29 - 3.55) (57). In a 20-year follow-up of adult men, baseline MetS was a predictor of developing CHD (RR = 1.64, 95% CI = 1.41 - 1.90), stroke (RR = 1.61, 95% CI = 1.26 - 2.06), and type 2 diabetes (RR = 3.57, 95% CI = 2.83 - 4.50); however MetS could not predict CHD as well as the Framingham risk score (58). Overall, current evidence indicates that MetS can be used as a simple and useful predictor of future risk of CVD and type 2 diabetes; however MetS seems to be a more accurate tool for identifying individuals at risk of type 2 diabetes.

4. Conclusions

This review indicates high incidence of MetS in Tehranian adults and adolescents, in which related factors like age and gender play a pivotal role. Increased WC was a strong predictor of MetS both in adults and adolescents. All definitions of MetS predicted cardiovascular disease and diabetes.

More information about time trends of MetS is needed, in addition to a comprehensive understanding of the genetic determinants of MetS.

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Footnotes

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Legacy of the Tehran Lipid and Glucose Study: Chronic Kidney Disease

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Abstract

Context: Chronic kidney disease (CKD), is correlated with a substantial upsurge in mortality and morbidity worldwide. In this review, we aimed to review the 20-year-findings on CKD of the Tehran lipid and glucose study (TLGS).
Evidence Acquisition: We conducted a systematic review of all studies on CKD that had been performed in the context of TLGS.
Results: Age adjusted prevalence of CKD, according to estimated glomerular filtration rate (eGFR) assessed with the two abbreviated equations of the modification of diet in renal disease (MDRD) and the CKD epidemiology collaboration (CKD-EPI) were 11.3% (95% confidence interval (CI): 10.7, 12.0) and 8.5% (95% CI: 7.9, 9.1), respectively. Using MDRD equation, over a mean follow up of 9.9 years, the incidence density rates of CKD were 285.3 person years in women and 132.6 per 10000 person-years in men. Studies on the TLGS population documented that abdominal adiposity defined as waist circumference (WC) categories (P for trend < 0.02) and waist gain in men (hazard ratio (HR) = 1.7, CI: 1.3, 2.2) significantly affected CKD development. Also, CKD had a significant effect on coronary heart disease (CHD) only in participants with low body mass index (HR = 2.06; CI: 1.28, 3.31 and HR = 2.56; CI: 1.04, 6.31 in men and women, respectively). Moreover, CKD was among the strongest independent predictors of stroke (HR = 2.01, CI: 1.22, 3.33). Also, compared to diabetic patients, an abnormal ECG was more prevalent in moderate CKD (P = 0.02).
Conclusions: Increased waist circumference and waist gain (only in men) were associated with developing CKD in the TLGS population. CKD was an independent predictor of CHD (in lean individuals) and stroke.

Keywords: Chronic Kidney Disease (CKD), Tehran Lipid and Glucose Study (TLGS)

1. Context

Chronic kidney disease (CKD), is correlated with a substantial upsurge in mortality and morbidity worldwide. Importantly, there has been a rise in its prevalence and incidence all over the world (1). The kidney disease outcome quality initiative (K/DOQI) guideline, defines chronic kidney disease as either kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 (1.0 mL/s/1.73 m^2) for > 3 months (2).

A number of risk factors are known to affect CKD. They include female gender, age, anthropometric indices, smoking, diabetes mellitus, hypertension, and dyslipidemia. On the other hand, chronic kidney disease is associated with a number of metabolic and cardiovascular disorders. Also, electrocardiographic (ECG) changes are common in patients with CKD; however, there are still uncertainties about whether or not ECG disturbances can predict future cardiovascular events in these patients (3).

The aim of this study was to review the 20 years results of the Tehran lipid and glucose study (TLGS) on CKD and its association with metabolic and cardiovascular diseases.

2. Evidence Acquisition

We conducted a systematic review of all TLGS-based studies addressing chronic kidney disease. The terms "chronic kidney disease" AND "Tehran lipid and glucose study" were used to search in PubMed/Medline. All articles with the term "chronic kidney disease" in their title, subject or MeSh were included for the initial review. Since studies on nutrition issues as their main topic have been addressed elsewhere, we excluded all articles that had examined the relationship between CKD and nutrition from this review.

2.1. Definitions and Classification of CKD

GFR is estimated by a number of equations. One of the most commonly used ones is the abbreviated modification

of diet in renal disease (MDRD) equation. The equation is expressed as:

GFR = 186 × (SCr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.210 if African-American)

In this equation, GFR is expressed as mL/min per 1.73 m^2, and serum creatinine (Scr) is expressed as mg/dL (1). Although the MDRD equation is quite popular, the CKD epidemiology collaboration (CKD-EPI) equation estimate GFR more accurately in individuals with either normal, mildly reduced, or even elevated GFR. Moreover, the CKD-EPI equation has resulted in diagnosing fewer individuals with CKD and more precise risk estimation for mortality than the MDRD equation in extremely large and broad populations. Previous studies compared the values of directly measured and eGFR. Their results showed that the CKD-EPI equation to estimate the GFR has been the most recommended creatinine-based alternative method for directly measured GFR to categorize CKD and assessment of the related risk factors (4). Using the CKD-EPI equation GFR is estimated as:

eGFR (mL/min per 1.73 m^2) = 141 × minimum (Scr/κ, 1) α × maximum (Scr/κ, 1)-1.209 × 0.993 Age × 1.018 [if female], where κ = 0.7 for females and 0.9 for males, α = -0.329 for females and -0.411 for males (5). The classification of CKD by stages is precisely defined by criteria of the kidney disease outcome quality initiative (K/DOQI) (1).

3. Results

3.1. Prevalence

Using the abbreviated MDRD study equation, Hosseinpanah et al. found that prevalence of CKD was 18.9% (95% confidence interval (CI): 18.2, 20.6). Accordingly, they found age adjusted CKD prevalence to be 14.9% (CI: 14.2, 15.6). Risk factors correlated with CKD comprised of age (odds ratio (OR) = 1.1, CI: 1.0, 1.2), gender (reference, male) (OR = 3.1, CI: 2.6, 3.7), Body mass index (BMI) (OR = 1.5, CI: 1.3, 1.8 for BMI 25 to < 30, and OR = 1.6, CI: 1.3, 2.0 for BMI ≥ 30), increased waist circumference (OR = 1.2, CI: 1.1, 1.4), hypertension (OR = 1.2, CI: 1.1, 1.4), and dyslipidemia (OR = 1.3, CI: 1.1, 1.5) (1).

Another unpublished study aimed to estimate the prevalence of CKD through a cross-sectional study in a population selected from the Tehran lipid and glucose study (phase II) by calculating GFR using CKD-EPI and MDRD equations separately. Data of a population of 8602 participants (43.2% male) were analyzed. The population was consisted of relatively young individuals whose mean (± standard deviation (SD)) age was 43.89(± 15.36) years with median and interquartile rage (IQ) (25 - 75) of 42 and (32 - 55) years, respectively. Prevalence of CKD, defined by MDRD-based eGFR was 10.1% (CI: 9.5, 10.7), whereas the age adjusted prevalence of CKD was 11.3% (CI: 10.7, 12.0). Prevalence of CKD, defined by EPI-based eGFR was 9.3 % (CI: 8.7, 9.9); while age adjusted prevalence of CKD was 8.5% (CI: 7.9, 9.1). Prevalence of CKD employing both equations was estimated to be higher in women than men. It was remarkable that the CKD-EPI equation determined CKD prevalence to be higher in men but lower in women. Using both equations, prevalence of CKD increased with age and was highest in those aged ≥ 70 years (Figure 1). In multiple logistic regression analysis, the multivariate-adjusted ORs for dyslipidemia, older age, female gender and hypertension were statistically significant with presence of CKD, by both equations; ORs of diabetes mellitus, smoking and abdominal obesity were not statistically significant in any of the CKD populations. In addition, OR of BMI > 25 was statistically significant in EPI-based CKD whereas it did not reach statistical significance in CKD population based on the MDRD equation.

3.2. Incidence

Using the MDRD equation, Tohidi et al. found that during a mean follow up of 9.9 years, the incidence density rates of CKD were 285.3 per 10000 person-years in women and 132.6 per 10000 person-years men. Female gender was linked with increased risk of developing CKD. Independent predictors for CKD in women comprised of age, being single or divorced/widowed, known diabetes, hypertension (marginally significant), current smoking and eGFR; conversely, education (intermediate degree) and family history of diabetes lowered the risk about 40% (P < 0.05). For men, risk factors of CKD comprised of age, hypertension (P for interaction comparing with women < 0.05), eGFR, newly diagnosed diabetes and high normal blood pressure. On the other hand, the risk of CKD was lowered by abdominal obesity about 30% (marginally significant). In Iran, more than 2% of population develop CKD annually (6).

3.3. Risk Factors

To evaluate the effect of body mass index, waist circumference (WC) and waist-to-hip ratio (WHR) on developing CKD in adults, a study by Noori et al. examined a representative sample of 3107 CKD-free subjects including (1309 men), aged > 20 years, and followed them for 7 years. Results showed that during follow-up, 419 participants (13.5%) developed CKD. After multivariable adjustment for a number of variables including age, sex, smoking, menopause, blood pressure, prevalent and incident diabetes, and change in WC, waist circumference was positively associated with risk of CKD. On the other hand, the WHR was not an independent risk factor of CKD. Interestingly, baseline waist categories affected the rate of decline

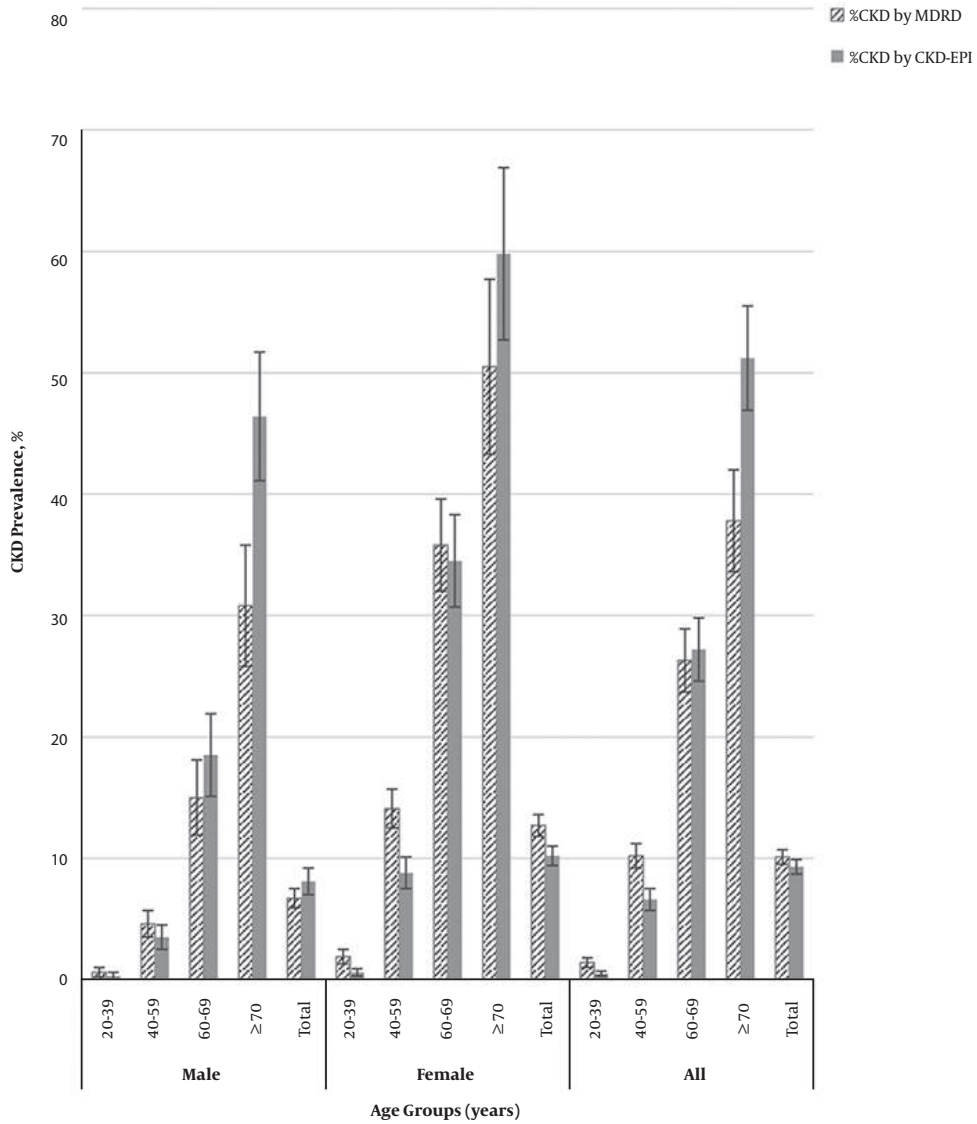

Figure 1. Chronic kidney disease (CKD) prevalence in different sex and age groups. Error bars denote 95% confidenceinterval. Abbreviations: MDRD, modification of diet in renal disease; CKD-EPI, CKD epidemiology collaboration.

in eGFR: Regression coefficient for 1 SD increase in WC was equal to -0.18 (CI: -0.28, -0.07). Accordingly, baseline WC was proved to be a better predictor of CKD than WHR ($P < 0.05$) or BMI ($P < 0.05$). The investigators concluded that comparing to WHR and BMI, waist circumference per se, was a more crucial determining factor of CKD risk in adults (7).

The relationship between chronic kidney disease and anthropometric measurements has been examined by several investigations, but the association between changes in waist circumference and incidence of CKD needs more clarification. In a study by Barzin et al., the effect of changes in WC on developing CKD was assessed in three consequent phases. A cohort of 8,183 CKD-free participants (46.5% men), mean age 47.4 years, were followed for 9 years. Four groups of waist changes were described: (I) Decrease in WC; (II) reference group; (III) mild to moderate increase in WC and (IV) severe increase in WC. Overall, mean MDRD based eGFR was higher in male participants (77.1 vs. 74.4

mL/min/1.73 m^2 in women, P < 0.001). A total of 1477 participants (1026 women) developed CKD during the follow-up. Their results showed that in women, changes in WC were not correlated with CKD incidence. In men, decrease in WC was not correlated with decreased CKD incidence (Hazard ratio (HR) = 0.90, CI: 0.6, 1.4), however, group III was associated with a 70% augmented risk of CKD (HR = 1.6, CI: 1.2, 2.2). Category IV also, was linked to a fourfold risk of CKD (HR = 3.7, CI: 2.7, 5.1). The authors concluded that WC changes were not independent determinants for CKD occurrence in women. In men however, waist gain negatively affected the CKD incidence (8).

To explore the association of metabolic syndrome (MS) and risk for CKD occurrence independent of diabetes, Rashidi et al. studied a cohort of 4607 diabetes/CKD- free adults (age > 18 years) in the context of the Tehran lipid and glucose study. Their results showed that 1010 (21.9%) participants had MS at baseline. During the follow-up of 3590 individuals, CKD occurred in 3.4% (n = 38) of the MS group and 2.0% (n = 73) of the non-MS group (OR = 1.88, CI: 1.26, 2.8). Excluding participants who had hypertension at baseline (n = 798), 406 individuals (10.7%) fulfilled the MS criteria. CKD developed in 62 (1.82%) subjects in the metabolic syndrome group and 8 (1.98%) in the non-MS group (OR = 0.925, CI: 0.446, 1.917; P = 0.844). These findings proposed that metabolic syndrome, as a constellation of risk factors, was a significant predictor for CKD. However, hypertension significantly affected this relationship (9).

In another study, Derakhshan et al. evaluated the effect of various combinations of blood pressure status and glucose tolerance on the occurrence of chronic kidney disease, type 2 diabetes mellitus (T2DM) and hypertension. They included 12808 Iranian adults in 3 separate analyses to examine the incidence of each above mentioned disease. Multivariate Cox proportional hazard models were employed for the analyses. During follow-up (median > 10 years), the incidence rate for CKD was 24.8 per 1000 person-years. Every category that comprised of hypertension (HTN) and/or T2DM possessed significant risk of developing CKD. However, the pre-diabetes/HTN group showed a slightly significant risk (HR = 1.19; CI: 0.98, 1.43, P = 0.06) (10).

In another study, Ramezankhani et al., analyzed the correlation between CKD and hypertriglyceridemic waist (HW) and waist-to height ratio (HWHtR) phenotypes. The median follow-up was 12.4 years. A total of 12,012 participants in the TLGS phases 1 and 2 were analyzed. For prospective analysis, the data of 8225 individuals (45% men) were included. Outcome was defined as development of CKD (eGFR < 60 mL/min/1.73 m (2). The HW phenotype was described as waist circumference (WC) > 90 cm in men and > 85cm in women, in the presence of triglyceride (TG) > 2.0 mmol/L. The HWHtR phenotype was identified as waist-to-height ratio (WHtR) > 0.5 and TGs > 2 mmol/L. In cross sectional analysis, both the HW and HWHtR phenotypes were linked with CKD in women ((adjusted OR = 1.37, CI: 1.01, 1.86, P < 0.05) and (adjusted OR = 1.58, CI: 1.03, 2.41, P < 0.05)), correspondingly. Conversely in men, while in non-adjusted and age-adjusted models both phenotypes were correlated with CKD, the associations were lost in fully adjusted models. In prospective analysis, neither of the phenotypes were significant risk factors of developing CKD. The investigators concluded that while in a cross-sectional setting, HW and HWHtR phenotypes were correlated with prevalent CKD, in prospective analysis, HW and HWHtR did not significantly predict CKD (11).

To determine the effect of various obesity phenotypes on the CKD incidence in adults, in a prospective study, Mottaghi et al. observed that rates of CKD-free MHO (metabolically obese but healthy) and MONW (metabolically healthy normal weight) obesity phenotypes were 75.3% and 60.6%, correspondingly (P < 0.0001). In model 1 (adjusted for age and sex) hazard ratios of developing CKD in MHO or MONW obesity phenotypes were 1.14 (CI: 0.91, 1.43) and 1.43 (CI: 1.09, 1.88), respectively. In model 2 (comprising of further adjustment for confounders) hazard ratios of CKD incidence in MHO or MONW obesity phenotypes were 1.23 (CI: 0.93, 1.62) and 1.43 (CI: 1.08, 1.90), correspondingly. The authors concluded that comparing with people with the MHO obesity phenotype, risk of incident CKD was higher in adults with the MONW obesity phenotype (12).

In a recent longitudinal study aiming to evaluate the risk of incident CKD in adults with abdominal obesity, participants aged > 20 years from TLGS phase II were enrolled. Abdominal obesity was defined as waist circumference > 89 cm in men and > 91 cm in women. Metabolic health was defined as having $\leq$ 1 component of metabolic syndrome, employing the joint interim statement (JIS) definition of metabolic syndrome. The study observed that from among 6597 individuals who entered the study, 1529 participants were affected by CKD after 10 years of follow up. Multivariate regression models demonstrated that, compared to metabolically healthy non-abdominal obese participants, men with the metabolically unhealthy non-abdominal obese phenotype had a slightly significant risk of developing CKD (HR = 1.38, CI: 0.96, 1.96, P = 0.08). However no statistically significant difference was observed for metabolically healthy abdominal obese phenotype (Unpublished data).

3.4. CKD and CVD

Population based studies have revealed inconsistent findings concerning the association between CKD and

CVD. To ascertain this association, the investigators examined the risk of CVD events in a sizable group of participants in the TLGS. A total of 6,209 CVD-free participants (mean age, 47.4 years) were followed up for 9.1 years. Among them, 22.2% (n = 1381) had MDRD based (eGFR < 60 mL/min per 1.73 m^2) at baseline. Ninety nine percent of them were in stage 3a. After adjustment for age and sex, the results showed that moderate renal insufficiency independently predicted CVD outcomes. However, its statistical significance was lost (HR = 1.14, CI: 0.91, 1.42) after further adjustment. Moreover, after categorizing the participants according to CKD status and BMI groups, no significant association was observed after further adjustment (P = 0.2). This study concluded that CKD did not independently predicted events. The increased prevalence of CVD in subjects with mild to moderate renal insufficiency in the TLGS population might have been due to the presence of other known CVD risk factors in this group (13).

Another prospective cohort with longer follow up duration was conducted to investigate the independent role of CKD in predicting CVD events. In this population-based cohort the CKD-EPI equation was used to estimate GFR and define CKDs. For this study, phase II of the TLGS study was selected for baseline measurements. CKD was defined as eGFR < 60 mL/min per 1.73 m^2. Of a total of 6185 participants with a median (IQ 25 - 75) follow-up of 10.2 (9.1 - 11.2) years, 3510 (56.8%) were women and 597 (9.7%) were diagnosed with CKD. The authors found that CKD was associated with future cardiovascular disease (CVD), especially in patients aged $\geq$ 55 years. This association was independent of well-known traditional CVD risk factors, i.e. hypertension, diabetes mellitus, hyperlipidemia, abdominal obesity, cigarette smoking, and family history of CVD. Furthermore, they reached a cutoff of 62 mL/min per 1.73 m^2 for future CVD events in their population (Unpublished data).

It has been reported that there are some interactions between CKD and other metabolic disorders including metabolic syndrome and obesity regarding coronary heart disease (CHD) outcomes; to address these interactions, Panahi et al. followed a total of 2823 men and 3684 women, aged $\geq$ 30 years, without cardiovascular disease for 10 years. Multivariable adjusted hazard ratios of CHD were estimated for those who developed CKD, MS or both by sex and body mass index levels (below and above 27 kg/m^2). In addition, interaction terms of CKD and MS and also CKD-MS components were assessed. Employing Cox proportional hazard models showed that chronic kidney disease without MS, had a significant effect on CHD only in participants with low body mass index (HR = 2.06; CI: 1.28, 3.31 and HR = 2.56; CI: 1.04 - 6.31 in men and women, respectively). In this subgroup, the combined effect of CKD and MS decreased to one-third of their multiplicative effect, showing that there was a negative interaction between CKD, MS, and obesity. Moreover, the same effect was spotted between CKD and hypertension in both sexes and CKD and type 2 diabetes mellitus in the men. The authors concluded that CKD independently predicted CHD only in non-obese individuals; however, its risk was vanished when joined to MS (14).

To examine the possible risk factors of stroke and their population attributable fraction (PAF), Fahimfar et al. designed a cohort study including 1089 men and 1289 women. The mean (SD) age for men and women was 61.1 (7.6) and 59.0 (6.7) years, respectively. Participants were followed for 9.3 years. To estimate the hazard ratio of each risk factor for stroke events Cox regression analysis with stepwise method was employed. A multivariate adjusted population attributable fraction (PAF) was calculated for any risk factors remaining in the model. During follow-up, stroke incidence rates was 4.5 (CI: 3.3, 6.0) and 2.5 (CI: 1.7, 3.6) in 1000 person-years for men and women respectively. The results showed that age $\geq$ 65 years (HR = 2.03, CI: 1.24, 3.31), male gender (HR = 2.00, CI: 1.16, 3.43), hypertension (HR = 3.03, CI: 1.76, 5.22), diabetes mellitus (HR = 2.18, CI: 1.34, 3.56), and chronic kidney disease (CKD) (HR = 2.01, CI: 1.22, 3.33) independently predicted stroke events. They observed that hazard ratio of CKD did not differ from other independent risk factors as proved by paired homogeneity test. The PAFs were 29.7% and 25% for male gender and age $\geq$ 65 years and 48.6%, 29.1% and 22.0% for hypertension, CKD and diabetes, correspondingly. The authors concluded that among modifiable predictors, CKD as well as hypertension and diabetes are the strongest independent predictors of stroke (15).

Rashidi et al. in another investigation, tried to determine whether chronic kidney disease and diabetes mellitus- independent of hypertension- had similar prevalence of ECG abnormalities. Data for 5942 men and women aged 30 to 69 years in the TLGS were collected. Minnesota ECG coding criteria were employed for coding ECG findings. The authors implemented the Whitehall criteria for abnormal ECG findings. Creatinine clearance (CrCl) was estimated using the Cockroft-Gault equation. Comparison was made between DM free subjects with moderate CKD and CKD free patients with DM. HTN prevalence was comparable in both groups. The findings showed that despite a similar prevalence of smoking, and a lower incidence of dyslipidemia and HTN, more than 19% of patients with CKD showed abnormal ECG findings, while prevalence of abnormal ECGs in diabetic patients were 14.7% (P = 0.02). The prevalence of Q waves was 11.5% in patients with CKD and 10.8% in patients with DM. In an age-matched subgroup of CKD-free diabetic patients, the prevalence of ECG abnor-

malities was comparable to that of DM-free patients with moderate CKD (19.3% vs 19.7%, P = 0.9). This study concluded that moderate CKD is a key predictor for development of ECG abnormalities and hence, is linked with ischemic heart disease. The significance of CKD as a predictor of ECG abnormalities is similar to diabetes mellitus. Patients with moderate CKD are potential candidates for meticulous CHD risk reduction (16).

4. Conclusions

In this review, we examined the TLGS-based studies that have assessed different aspects of CKD during the last two decades. The topics addressed by reviewed studies included prevalence and incidence of CKD, effect of obesity and its different phenotypes, WC and its changes as well as metabolic syndrome and its components on CKD. Also role of CKD in developing CVD, metabolic syndrome and stroke and ECG abnormalities in CKD were examined.

One important strength of aforementioned studies is the fact that they examined sizable number of individuals in the context of a population based study (TLGS). However, their limitations merit further comment. Regarding CKD prevalence and incidence, in one study authors had not obtained data on urinary albumin and protein. Therefore in this population, the prevalence of stages I and II CKD could not be estimated. Also a single creatinine measurement was accepted for estimating eGFR; therefore one cannot ascertain the persistence of CKD for at least 3 months. Furthermore, serum creatinine measurements were not calibrated to the Cleveland Clinic; Also the MDRD eGFR equation was not validated in the local population, which could have caused an overestimation in the prevalence of CKD. Considering the association between obesity for CKD, a study pointed out probable misclassification of CKD due to using eGFR and the possible effect of greater muscle mass in individuals with higher BMI. Another study mentioned the overall young study population as its limitation for assessing the relationship between metabolic syndrome and CKD. And last but not least, studying the risk factors for ischemic stroke, one study listed different types of public and private healthcare systems as a barrier to detect all cerebrovascular events in district 13 of Tehran.

Results of the reviewed studies showed that age adjusted prevalence of MDRD-based and EPI-based CKD, were 11.3% (CI: 10.7, 12.0) and 8.5% (CI: 7.9, 9.1), respectively. Over a mean follow up of 9.9 years, the incidence density rates of MDRD based-CKD were 285.3 and 132.6 per 10000 person-year, among women and men, correspondingly. Assessing risk factors of CKD, studies conducted on the TLGS population documented that abdominal adiposity defined as waist circumference (WC) categories (P for trend < 0.02) and waist gain in men (HR = 1.7, CI: 1.3, 2.2), significantly affected development of CKD. With regard to the association between CKD and cardiovascular diseases, it was shown that CKD had a significant effect on coronary heart disease (CHD) only in participants with low body mass index (HR = 2.06; CI: 1.28, 3.31 in the men and HR = 2.56; CI: 1.04, 6.31 in the women). Moreover, it was reported that, CKD was amongst the strongest independent predictors of stroke (HR: 2.01, CI: 1.22 - 3.33). Also, compared to diabetic patients, moderate CKD was a main risk factor for the development of the abnormal ECG (P = 0.02).

In conclusion, the reviewed studies showed that in the TLGS population, increased waist circumference and waist gain (only in men) were associated with CKD development which was also an independent predictor of CHD (in lean individuals) and stroke.

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Genetic Identification for Non-Communicable Disease: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: Tehran Lipid and Glucose Study (TLGS), a longitudinal family based cohort study, is the oldest and largest longitudinal family based study in Iran, aimed at investigating effects of environmental, social and biological factors on the health of Tehranians over time. Considering the importance of genetic studies in this aspect, here we present a summary of the important genetic findings, and the potentiality of their contributions to future related projects.
Evidence Acquisition: For all related studies during the past 20 years the search sources were all prominent search engines such as PubMed, Scopus, and Google Scholar with the most proper Medical Subject Headings (MeSH).
Results: This review summarizes associations of 6 binary phenotypes and 17 quantitative traits with genetic markers in 26 genes. Of the 47 genetic markers, studied most were related to cardio metabolic risk factors. Results of heritability and linkage analysis were also collected and the highest heritability was found to be related to HDL-C (0.5).
Conclusion: Considering the opportunity provided by large-scale cohort studies to investigate molecular effects of genetic variants on causality and different omics' data, genetic studies conducted on TLGS population have had a remarkable success in identifying genetic variants that facilitating a unique genetic database on Iranian populations. The results of genome wide association studies in this population are currently facilitating investigations to define the Iranian genetic differences with other population.

Keywords: Tehran Lipid and Glucose Study, Tehran Cardio-Metabolic Genetic Study, Genetic Association, Heritability

1. Context

Research of common diseases, currently uses analysis of genetic data available on the functioning of human genome, as the primary most reliable tool for determination of new variants of this genome (1). In addition to genetic variants, environmental and behavioral changes also play an important role in the development of chronic diseases. Therefore, in association studies, gene-environment interactions or presence of a particular environmental exposure, are being strongly emphasized (2). In some situations, populations are related to a lot of exposures in different ways which cause to adjust the effect of specific genetic variants; the resulting interactions can prevent the detection of a genetic effect (3). Collection of pre-morbid exposure can be allowed to standardize by the prospective cohort design. Identifying genomic variations in participants improves the power of these studies. Assessment of environmental risk factors and analyzing gene-environment interactions would provide solid data, less prone to bias and easily extrapolatable to the entire population, compared to case-control studies.

This review highlights some of the important findings documented on genetic cardio metabolic risk factors investigated in the Tehran Lipid and Glucose Study (TLGS) over twenty years.

2. Evidence Acquisition

The search sources for covering a complete range studies were all prominent search engines such as PubMed, Scopus, and Google Scholar with the most proper Medical Subject Headings (MeSH) during the past 20 years.

3. Results

3.1. Project Description

TLGS is a prospective ongoing family based cohort study, conducted on over 15,000 individuals, aged 3 years,

enrolled in Phase 1 and followed every 3.5 years since 1999 (4). Other individuals from different pedigrees were also added to the cohort during the follow-up period. Hence, after 20 years of follow-up (2017), 23259 individuals of 5434 households had participated in the study (5). At each visit, subjects signed a consent form and were interviewed to document demographic data including marriage status and spouse information, and were then referred to trained physicians for clinical examinations of the anthropometric and cardiovascular risk factors; they were also referred to laboratories for blood sampling for extraction of sera and DNA. Composition and familial relationship have been described elsewhere (5).

3.2. Heritability and Aggregation

In the present project, the heritability of metabolic syndrome, obesity and lipid profiles of TLGS families were estimated after age and sex adjustment (Table 1) (6, 7). The highest heritability was for HDL-C (about 50%) and the lowest was for metabolic syndrome (15%). Metabolic syndrome components were investigated using exploratory factor analysis (EFA) and results showed that three important factors, including blood pressure, lipids, and obesity in conjunction with fasting blood sugar are the sub components of the metabolic syndrome with heritability of around 6.14 and 7%, respectively (7).

Moreover, familial aggregation of the metabolic syndrome components was studied unmarried adolescents who had at least one parent with available information. Results showed a strong correlation between risk of metabolic syndrome in children and parents and significant differences in means of triglycerides, HDL-C and body mass index between children of parents with metabolic syndrome and those whose parents were metabolic syndrome free (8).

Table 1. Estimated Heritability for Studied TLGS Phenotypes

Cardiometabolic Risk Factors	Mean Heritability[a], %	P Value
Lipids		
HDL-C	0.5	8.7×10^{-129}
TG	0.36	1.1×10^{-36}
FBS	0.29	Less than 0.05
SBP	0.25	Less than 0.05
DBP	0.26	Less than 0.05
LDL	0.33	4.2×10^{-64}
Total cholesterol	0.32	1.8×10^{-61}
Non-HDL-C	0.3	1.9×10^{-55}
Obesity		
BMI	0.3	7.3×10^{-19}
WC	0.27	Less than 0.05
WHR	0.27	8.0×10^{-17}
Waist circumference	0.32	9.1×10^{-22}
REE	0.26	4.6×10^{-12}
Hip	0.21	1.6×10^{-10}
Height	0.23	2.4×10^{-13}
Weight	0.33	6.9×10^{-24}
Body size	0.51	5.9×10^{-47}
High BMI	0.57	5.8×10^{-6}
Abdominal obesity	0.48	1.1×10^{-13}
High WHR	0.33	0.1×10^{-6}
Metabolic syndrome		
Metabolic syndrome score	0.15	Less than 0.05

Abbreviations: HDL-C, high density lipoprotein; TG, triglycerides; FBS, fasting blood sugar; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio; REE, resting energy expenditure.
[a]Heritability estimation adjusted for age and sex.

3.3. Genetic Association Studies

Genetic association studies, powerful tools used in investigating the correlation between disease status and genetic variation, are helpful in identifying candidate genes or genomic regions that contribute to a specific complex disorder (9). Usually, the candidate genomic regions for different studies are selected based on the results of previous studies, especially previous genome wide association studies conducted on the same population or on other similar populations. Here, we described the most important genetic findings of studies conducted on TLGS participants since 1999.

3.4. Lipid Metabolism

Low HDL-C concentration is the most frequent lipid related risk factor in Iran (10). Some missense mutations in ABCA1 (ATP binding cassette subfamily a member 1), APOA1 (apolipoprotein A1), APOE (apolipoprotein E), APOA5 (apolipoprotein A5), and SCARB1 (scavenger receptor B1) showed significant associations with decrease of HDL-C (11-18); other HDL-C related variations were observed in the splice site, intronic, upstream and downstream regions. The most studied intronic variations in the CETP gene in different populations are rs753562256 (TaqI) and rs708272 (-629A/C) (19). In TLGS participants, allele frequencies were 0.382 for the TaqI B2 and 0.462 for the -629A/C A. In addition, linkage disequilibrium analysis showed that TaqI B1 and B2 alleles and the alleles of the-629A/C variant were in linkage disequilibrium in our population (D = 0.0965 and 0.4695, respectively). There was a significant association between the presence of B2 and A alleles with higher HDL-C concentration and low CETP activity (20, 21).

In 2012, the effects of two polymorphisms, rs63750792

and rs2070665 were studied in the TLGS population and significant associations were found between triglyceride, HDL-C, HDL_2, and levels of Apo AI and Apo B (14). Some years later, Bandarian et al. in an exon and promoter sequence analysis conducted among 63 individuals according to 95th percentile of HDL-C (extremely high) on apolipoprotein A1; their sequencing results showed 42 common and rare variants. Exonic variants included eleven missense, six synonymous, and one nonsense (13).

Regarding the huge effect of the APO gene cluster on lipid profile measurements and the large number of genes in this family, XbaI Apo lipoprotein B polymorphisms were found to have a significant association with increased total cholesterol and Apo lipoprotein B in a cross-sectional study of 849 TLGS participants, associations that remained significant even after adjusting for demographic and blood covariates i.e., age, sex, body mass index, smoking, diastolic and systolic blood pressure, and fasting blood sugar (22).

Mutations in the LDL-R (low density lipoprotein receptor) gene could lead to autosomal dominant disorder, familial hypercholesterolemia. In this gene, the splice region variant rs72658867-A and rs17248748-T in intron 14 and intron 1 are associated with lower non-HDL-C levels and confer protection against CAD. Retention of intron 14 during transcription is caused by the LDLR splice region variant, rs72658867-A, located at position +5 in intron 14 (NM-000527: c.2140 + 5G > A) and can appear a truncated LDL receptor lead to mainly lacked functions of the receptor. This retention of the intron characterizes almost half of the transcripts generated from chromosomes carrying rs72658867-A. Also, in spite of the wild type transcripts do not exceed levels in non-carriers the same variant increases LDLR mRNA expression and this demonstrated that the sequence variants disrupt the LDL receptor can lower non-HDL-C and protect against CAD (23).

One of the well-known variations related to HDL-C concentration is rs1800588 (-514C/T), which may influence HDL-C (24); generally, the (T) allele is considered to lead to higher HDL-C levels. The "T" allele non-carriers in the -514C/T polymorphism of the LIPC gene have lower level of HDL-C than carriers.

SRBI or SCARB1 (scavenger receptor class B member 1) is a key component in reverse cholesterol transportation. In a study conducted to assess the association between lipid profiles and rs4238001 polymorphism through the SR-BI gene among the TLGS residents, minor allele frequency of the polymorphism of SR-BI gene was 0.159 (18); in addition, the association of rs4238001 with HDL-C and HDL-3 was not significant except after adjusting for age. The result of this study showed that age has a confounder role which could regulate the strength of association between the single nucleotide polymorphism of SR-BI and HDL-C level trait (18).

Relationships of the LCAT (lecithin-cholesterol acyltransferase) gene with lipid profiles have also been investigated. Through this study, the promoter, coding regions and exon/intron boundaries of LCAT were amplified. As a result, sequenced in consecutive individuals (n = 150) who had hardly low or high HDL-C levels with no other major lipid abnormalities; 14 single-nucleotide polymorphisms (SNPs) were determined included 10 novel SNPs. Three of the novel variations (position 5,151 in exon 1, position 6,531 in exon 5, and position 6,696 in exon 5) are caused by an amino acid substitution. However, results did not show very strong associations between recognized variants and HDL-C (25). Also, a replicate study conducted on rs5923 polymorphism of the LCAT gene showed no associations with low HDL-C levels in an Iranian population (26).

3.5. Metabolic Syndrome

Genetic studies of the metabolic syndrome in the TLGS, use one of the three following definitions: (1) "National Cholesterol Education Program Adult Treatment Panel III (ATP III)" (27), (2) International Diabetes Federation (IDF) (28) and (3) The Joint Interim Statement (JIS) (29). Furthermore, based on national reports, Azizi et al. suggested a waist circumference cutoff $\geq$ 95 cm for those aged above 16 years, and WC > 78 cm for those aged between 10 - 16 year (30).

Association studies of genetic markers in the APO gene cluster regions with dietary patterns conducted on patients with metabolic syndrome showed that the rs5128 is associated with different nutrient components in metabolic syndrome affected individuals (31, 32).

Moreover, the relation of variation rs5110 (G360T) with metabolic syndrome has been evaluated in a case/control study (16). Results showed that APOA5 rs2075291 could play an important role in triglyceride and HDL-C levels in individuals affected with metabolic syndrome, although the association of APOA5 rs662799 polymorphism with these levels is still under debate (33).

CD36 (CD36 Molecule), MC4R (melanocortin 4 receptor), and SLC30A8 (solute carrier family 30 member 8 (ZnT-8)) are other important genes that have been reported to be associated with metabolic syndrome in TLGS families (34).

3.6. Obesity

CVD risk factors of obesity have a high heritability as shown in Table 1. Many loci have been reported to be associated with obesity risk factors worldwide. Obesity related genetic regions focused on the effect of the 16q12.2 region, which contains the FTO (fat mass and obesity-associated protein), IRX (iroquois-class homeodomain protein), and MMP (matrix metallopeptidase) family genes, FABP2 (fatty acid binding protein 2), ADRB3 (adrenoceptor beta 3), IL6 (interleukin 6), PPAR-γ (peroxisome proliferator-activated receptor gamma), TNF (tumor necrosis factor-alpha), and CCND2 (cyclin D2) genes.

The chromosomal region 16q12.2 contains the most obesity related genes. Various GWA and Meta GWA have provided clear evidences confirmed that FTO is associated with body mass index, and affects dietary intakes and preferences for certain energy-dense foods, as well (35) (Figure 1). In a study conducted on 6928 unrelated subjects with 986 genotyped SNPs located on the 16q12.2 regions, significant SNP sets were relatively denser in the introns of FTO, AIKTIP, and MMP2 genes and near IRX3 gene (Figure 1) (35). Although previous studies confirm the association between rs1421085, rs1121980, rs1558902, and rs8050136 in the first intron of the FTO gene and body mass index, this review showed no association between FTO variants and body mass index in healthy metabolic obese (HMO) individuals (36). FABP2 genes are thought to play a role in the intracellular transport of long-chain fatty acids and their Acyl-CoA esters and may help in maintaining energy homeostasis by functioning as a lipid sensor. Examining a missense variant (rs1799883) on the FABP2 gene among individuals with body mass index $\geq$ 30 Kg/m^2 showed no significant differences between case and control groups in terms of allele frequency (37).

In the ADRB3 gene, an association was found between variations in rs4994 and obesity in TLGS population (38). A case-control study examining the relation of rs1801282 polymorphism in the PPAR-γ gene with obesity in 479 participants the TLGS indicated that the presence of G allele could lead to a 1.7 fold increase in the risk of obesity (39).

Regarding previous studies, elevated TNFα levels are linked to obesity and insulin resistance in some populations; the association of obesity with rs1800629 and rs361525 (in the promotor region) was investigated in an adult Iranian population and results showed that these SNPs were not an important risk factor for obesity or consequently for cardiovascular disease (40).

CCND2 encodes a G1/S cell cycle regulator and is the key regulator of postnatal pancreatic β cell mass (41). This cyclin forms a complex with CDK4 or CDK6 and functions as a regulatory subunit of the complex, whose activity is required for cell cycle G1/S transition. In the TLGS population, a variant with low frequency of 1.47% in intron 1 of CCND2 gene, rs76895963, showed significant associations with both increased height and body mass index showed significant associations with both increased height (1.17 cm per allele, P = 5.5 $\times$ 10^{-12}) and body mass index (0.56 kg/m^2 per allele, P = 6.5 $\times$ 10^{-7}). Moreover, the G allele of this variant reduces risk of type II diabetes by 50% (odds ratio (OR) = 0.53 (P = 5.0 $\times$ 10^{-21})) (42).

3.7. Diabetes

In accordance with the definition provided by the American Diabetes Association, adult participants are considered to have diabetes if they meet at least one of the following criteria: FPG $\geq$ 126 mg/dL, or 2h-PCPG $\geq$ 200 mg/dL or taking anti-diabetic medication (43). In addition to TCF7L2 (transcription factor 7 like 2) and HHEX, which encode for proteins implicated in blood glucose homeostasis, the effects of PDX1 (pancreatic and duodenal home box 1) and PAM (pancreatic and duodenal homeobox1) genes on type II diabetes (T2D) in TLGS families were investigated.

The PAM gene encodes a multifunctional protein; two missense variants in this gene carrying p.Asp563Gly (with frequency of 4.98% and OR = 1.23, P = 3.9 $\times$ 10^{-10}) and p.Ser539Trp (with frequency of 0.65%, OR = 1.47, P = 1.7 $\times$ 10^{-5}), allow moderately higher risk of T2D (42).

A transcriptional activator of several genes account for insulin, somatostatin, glucokinase, islet amyloid polypeptide, and glucose transporter type 2 is encoded a protein by PDX1. In our population a rare (0.20%) frameshift variant in PDX1, carrying p.Gly218Alafs*12, demonstrated an association with high risk of T2D (OR = 2.27, P = 7.3 $\times$ 10^{-7}) (42).

3.8. Thyroid

Previous studies confirm our findings on the association between TPO (thyroid peroxidase) gene polymorphisms with both anti-TPO and anti-TG factors. TPO or iodide peroxidase is a key enzyme expressed in the thyroid for hormone foundation. TPO catalyzes oxidation of iodide ions to iodine atoms that form iodothyronines in a thyroglobulin (Tg) molecule for the production of thyroxine (T4) or triiodothyronine (T3) hormones (44). Serum autoantibodies in patients with Graves' disease or Hashimoto's thyroiditis recognized the TPO that is the major thyroid autoantigen (45). The TPO is a membrane-bound glycoprotein and which in humans, consists of 933 amino acids that are encoded by the mRNA of 3048 nucleotides. The TPO gene consists of 17 exons and extends over 150 kb on the short arm of chromosome 2, locus 2p25. According to molecular genetic studies, mutations in this gene are associated with one of the most common causes of autoimmune thyroid diseases i.e. autosomal recessive inheritance (46, 47). Autoimmune thyroid diseases result from the interaction of several mechanisms, including total absence of TPO activity, inability of TPO to bind to the hem cofactor, inability to interact with the Tg substrate, and abnormal sub cellular localization, all of which are affected by various mutations in the TPO gene. Of TPO gene variations, the associations of C2145T (rs732608), G1193C (rs2175977), and A1936G (rs10189135) polymorphisms with anti-TPO levels were evaluated in the TLGS population. Results showed that the C allele polymorphism in the synonymous variant C2145T of exon 12 is associated with high levels of serum anti-TPO and that carriers of this allele are predisposed to autoimmune thyroid disease 9.2 fold higher than those, who have no C allele. Moreover, missense variant G1193C of exon 8 has no effect on increased levels of anti-TPO (48), although, in the missense variant A1936G of exon 11, the G allele is significantly associated with in-

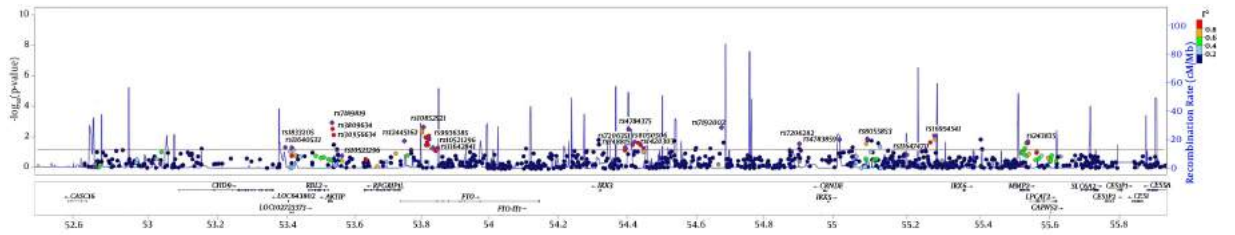

Figure 1. Regional association plot shows the P values (-log P values) of each SNP and recombination rate in the 16q12.2 region. The red line is related to -Log (0.05), indicating significance level. For each significant set, SNP with the lowest P value is determined (35).

creased anti-TPO levels (49); all the above results suggest that the rs732608 and rs10189135 polymorphisms are associated with high levels of anti-TPO in this population (49).

3.9. Polycystic Ovary Syndrome (PCOS)

The most prevalent endocrinopathy in female is PCOS. This disorder affects 6% - 10% of caucasian premenopausal women (50), with a reported prevalence of 7% among Iranian women, based on the NIH definition (51).

Associations between PCOS and variations in three different genes, TCF7L2, HHEX, and VDR (vitamin D receptor) have been investigated. TCF and HHEX genes have been implicated in blood glucose homeostasis and genetic variants of this gene are associated with increased risk of T2D. Given the simultaneous occurrence of PCOS and T2D (indicating a common underlying genetic etiology) (52), the association between IR and two strongly T2D associated gene variants (rs7903146 in TCF7L2, and rs1111875 in HHEX) is affected by PCOS status in Iranian women. After adjustment for age and body mass index, a protective effect of the HHEX A allele is observed on the risk of IR in non-PCOS subjects (confidence interval (95%): 0.33 - 0.78; P = 0.002) (52).

The VDR gene encodes the nuclear hormone receptor for vitamin D3. A single nucleotide polymorphism rs757343 in the initiation codon were studied (53-55) and the results showed that presence of the A allele was associated with a 74% increased risk of severe phenotype development (OR, 1.74; 95% CI, 1.07 - 2.82) while no association was observed with disease risk.

3.10. Hip Osteoarthritis and CHADL Gene Variant

The CHADL (chondroadherin like) in the 22q13.2 region is a negative modulator of the chondrocyte differentiation. In an Iranian population the allele frequency of a frameshift mutation, rs532464664 (p. Val330Glyfs*106) was 0.0115 and 23 of the studied individuals were heterozygous for this variation (56).

3.11. Tehran Cardio Metabolic Genetic Study (TCGS)

Considering the importance of genome wide association studies, exome sequencing and whole genome analyses, TCGS was designed in collaboration with the Research Institute for Endocrine Sciences (RIES) and the deCODE genetics company. The TCGS cohort comprises 17,186 (86.3%) of the 19,905 TLGS participants who provided baseline blood samples for plasma and DNA analysis. This study comprises of 849 independent individuals and 3109 families with at least one member with complete genotype data. Studies took account into the TCGS have been being navigated to determine relevant specimen of genetic polymorphisms that could be associated to cardio-metabolic risk factors in Tehran. TLGS database, the oldest and biggest Iran cohort, includes clinical, behavioral, and biochemical data for the whole participants. After augmenting this study by starting TCGS project and appending genome-wide data to the TCGS database, the study would be capable to consider gene-gene and gene-environment interactions and their relation to disease status (5).

4. Conclusions

Iran is a large country with diverse ethnicities, with a high rate of consanguineous marriage in some regions resulting in high inbreeding rates and different ethnicities and complex genetic pattern for this population. Considering that, Tehran, the capital city of Iran, has diverse ethnicities and cultures, the TLGS population could provide us with valuable information on Iranian populations. Since, these individuals have been followed for at least 20 years, their phenotype and genotype variations, in addition to their outcomes provide us with good infrastructure for research, the findings of which could shed more light on non-communicable disorders. A summary of genetic association studies has been shown in Table 2 and Figure 2A and 2B. Totally 48 variations in 26 genes in relation to the phenotypes were studied in the TLGS. Among them, 34% of studied variants were in coding consequences, and 20 of them were missense variants. Currently, all participants of the TCGS are chip-typed and over 1000 individuals have been genome sequenced. Data of the TLGS and related studies not only add to current knowledge on genomic differences between Iranian populations and other countries but also recommend new strategies for early preven-

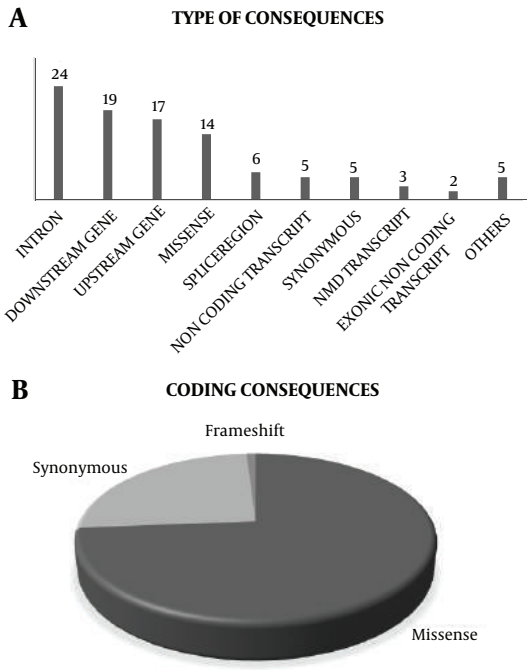

Figure 2. A, All genetic variation consequences studied in TLGS; B, coding consequences studied in TLGS (35)

tion and treatment of non-communicable diseases. Moreover, results of the TLGS delineate the path to personalized medicine and predictive medicine, which benefit both individuals and governments providing cost-effective treatments and increasing the quality of life especially in elderly patients.

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Table 2. Studied Polymorphisms in TLGS

Symbols	SNP	Location (Allele)	Consequence	Codons (Amino acids)	Studied Phenotypes/Traits	Sample Size	References
ABCA1	rs2230806	9: 104858586 (T)	Missense	aGg/aAg (R/K)	Cholesterol, triglyceride, HDL-C, apolipoprotein A1, apolipoprotein B	823, 778	(11)
ADRB3	rs4994	8: 37966280 (G)	Missense	Tgg/Cgg (W/R)	Obesity, BMI	401	(38)
APOA1							
	rs2070665	11: 116836968 (G)	Downstream	-	Extreme high and low HDL	132	(12, 13)
	rs121912724	11: 116836361 (C)	Missense	cTg/cGg (L/R)	Extreme high and low HDL	132	(12, 13)
	rs201148448	11: 116837080 (A)	Missense	Gtg/Ttg (V/L)	Extreme high and low HDL	132	(12, 13)
APOA2							
	rs6413453	1: 161222526 (A)	Splice region, Intron	-	Extreme high and low HDL	132	(12, 13)
	rs5069	11: 116837538 (A)	Intron	-	Cholesterol, triglyceride, HDL-C, apolipoprotein A1, dietary pattern	823, 828	(32, 57)
	rs670	11: 116837697 (T)	5-prime-UTR	-	Cholesterol, triglyceride, HDL-C, apolipoprotein A1, dietary pattern	823, 828	(32, 57)
	rs5082	1: 161223893 (A)	Upstream	-	Extreme high and low HDL	132	(12, 13)
APOA3	rs5128	11: 116832924 (C)	Downstream	-	Cholesterol, triglycerides, HDL-C, apolipoprotein A1, Dietary fatty acids, dietary pattern, metabolic syndrome	823, 1510, 828	(32)
APOA5							
	rs662799	11: 116792991 (A)	Upstream	-	Metabolic syndrome, HDL-C	947	(16, 58)
	rs2075291	11: 116790676 (A)	Missense	Ggc/Tgc (G/C)	Metabolic syndrome, HDL-C	947	(16, 58)
	rs3135506	11: 116791691 (A)	Missense	tCg/tTg (S/L)	Metabolic syndrome, HDL-C	947	(16, 58)
APOB	rs693	2: 21009323 (A)	Synonymous	acC/acT (T)	Cholesterol, triglyceride, HDL-C, apolipoprotein B	849	(14)
APOE							
	rs7412	19: 44908822 (T)	Missense	Cgc/Tgc (R/C)	HDL-C, LDL-C, obesity, BMI	1030, 843	(17, 59)
	rs429358	19: 44908684 (C)	Missense	Tgc/Cgc (C/R)	HDL-C, LDL-C, obesity, BMI	1030, 843	(17, 59)
CCND2	rs76895963	12: 4275678 (G)	intron	-	Diabetes, height, BMI	1,624 cases, 9,163 controls	(42)
CD36							
	rs10499859	7: 80629494 (G)	Intron	-	Metabolic syndrome, HDL-C	337	(34, 60)
	rs13246513	7: 80677435 (G)	Downstream	-	Metabolic syndrome, HDL-C	337	(34, 60)
CETP							
	rs708272	16: 56962376 (A)	intron	-	Cholesterol, triglycerides, HDL-C	1021, 555	(20, 21)
	rs1864163	16: 56963321 (A)	Intron	-	Cholesterol, triglycerides, HDL	1021, 555	(20, 21)
CHADL	rs532464664	22: 41238083 (in-sCGCGCGCC)	Frameshift mutation	gtg/gGGCGCGCGt (V/GRAX)	Hip osteoarthritis	996	(56)
FABP2	rs1799883	4: 119320747 (A)	Missense	Act/Tct (T/S)	Obesity, BMI	400	(61)
FTO							

	rs1421085	16: 53767042	Intron	-	BMI, MUHO	945	(62)
	rs1558902	16: 53769662	Intron	-	BMI, MUHO	945	(62)
	rs1121980	16: 53775335	Intron	-	BMI, MUHO	945	(62)
	rs8050136	16: 53782363	Intron	-	BMI, MUHO	945	(62)
HHEX	rs1111875	10: 92703125 (T)	Intergenic	-	PCOS	504	(52)
IL6	rs1800795	7: 22727026 (G)	Intron	-	Obesity, BMI	214	(63)
LCAT	rs5923	16: 67940050 (A)	Synonymous	Ctg/Ttg (L)	HDL-C	130	(64)
LDLR							
	rs200238879	19: 11105602 (C)	Splice region, intron	-	Non-HDL, triglycerides, HDL-C	9,631	(23)
	rs17248720	19: 11087511 (T)	Upstream	-	Non-HDL, triglycerides, HDL-C	9,631	(23)
	rs17248748	19: 11095364 (T)	Intron	-	Non-HDL, triglycerides, HDL-C	9,631	(23)
	rs72658867	19: 11120527 (A)	Splice region, intron	-	Non-HDL, triglycerides, HDL-C	9,631	(23)
LIPC	rs1800588	15: 58431476 (T)	Upstream	-	Cholesterol, triglycerides, HDL-C	1021, 555	(65)
MC4R	rs12970134	18: 60217517 (A)	Intergenic	-	Dietary pattern, metabolic syndrome	815	(66, 67)
PAM							
	rs35658696	5: 103003107 (G)	Missense variant	gAt/gGt (D/G)	Diabetes	1,624 cases, 9,163 controls	(42)
	rs760687925	1: 204973276 (G)	Missense, splice region	tCg/tGg (S/W)	Diabetes	1,624 cases, 9,163 controls	(42)
PPAR-γ	rs1801282	3: 12351626 (G)	Missense	Cca/Gca (P/A)	Obesity, BMI	239	
SCARB1	rs4238001	12: 124863717 (T)	Missense	Ggc/Agc (G/S)	Cholesterol, triglycerides, HDL	774	
SLC30A8	rs13266634	8: 117172544 (T)	Missense	Cgg/Tgg (R/W)	Dietary patterns	816 case and 816 control	
TCF7L2	rs7903146	10: 112998590 (T)	Intron	-	Diabetes	11000	
TNF							
	rs1800629	6: 31575254 (A)	Upstream	-	Obesity, BMI	244	
	rs361525	6: 31575324 (A)	Upstream	-	Obesity, BMI	244	
TPO							
	rs732608	2: 1496127 (C > T)	Synonymous variant	(Pro715)	Weight, Anti- TPO, Anti-Tg	184	
	rs2175977	2: 1477459 (G > C)	Missense variant	(S/T)	Weight, Anti- TPO, Anti-Tg	184	
	rs10189135	2: 1493885 (A > G)	Missense variant	(V/M)	Anti TPO, weight	190	
VDR							
	rs757343	12: 47845892 (T)	Intron	-	PCOS	260	
	rs1544410	12: 47846052 (T)	Intron	-	PCOS	260	

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Health-Related Quality of Life in Tehran Lipid and Glucose Study

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Abstract

Context: Beyond the objective outcomes of metabolic syndrome (MetS), the association between this syndrome and its patient-centered outcomes need to be investigated in Middle-Eastern countries. This report aims to summarize the Tehran lipid and glucose study (TLGS) findings regarding the association between MetS and health-related quality of life (HRQoL) and its influential factors through the past decade.

Evidence Acquisition: The current review has been conducted on the TLGS published data regarding different aspects of the association between MetS and HRQoL in adult participants through the last decade. To assess HRQoL, the Iranian version of short form health survey (SF-36) was used. To define MetS the most commonly used insulin resistance (IR)-and waist circumference (WC)-based MetS definitions have been applied in the publications reviewed.

Results: As a whole, MetS was a determinant of poor physical HRQoL only in women (OR: 1.78; 95% CI: 1.21 - 2.61), particularly in those with more component of MetS ($P < 0.001$). Results further showed that only reproductive aged women with MetS were more likely to report poor PCS compared to those without MetS even after adjusting for age (OR: 1.7, 95% CI: 1.0 - 3.0; $P < 0.05$). Different structures of MetS and physical HRQoL constructs in men and women as well as age and smoking with significant gender-specific effects on mental HRQoL were factors responsible for the gender specific pattern observed. Considering the duration of MetS, only women with intermittent MetS indicated higher risk for reporting poor PCS (OR: 2.75, 95% CI: 1.19 - 6.37; $P < 0.001$) compared to those without MetS. The observed sex-specific pattern used to detect poor HRQoL in those with MetS was confirmed by all WC-based definitions except for the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) definition. However, none of IR-based definitions could detect poor physical and mental HRQoL in either gender.

Conclusions: In summary, in the TLGS population, the association between MetS and HRQoL followed a sex specific pattern, mainly significant only in women and in the physical aspect.

Keywords: Metabolic Syndrome, Health-Related Quality of Life, TLGS

1. Context

The metabolic syndrome (MetS), as a complex of metabolic abnormalities could directly increase the risk of cardiovascular diseases (CVDs) and diabetes type 2 (1, 2), with a prevalence fast increasing in different populations in both the developed and developing countries (3-7). Although national data on Iranian adults indicates a decreased prevalence of MetS from 35.9% in 2007 to 32.9% in 2011 (8), it is still a considered a major health problem in our population.

Considering the World Health Organization (WHO) definition of health (9) and revolution in the medical framework of prevention and treatment of non-communicable diseases (10, 11), improving health care and health-related quality of life (HRQoL) has become the ultimate goal of health promotion programs, beyond increasing the individuals' life expectancy (12, 13). As a patient-centered outcome, HRQoL refers to individuals' own perceptions of their health status and life satisfaction (13, 14). Beyond the objective outcomes of MetS such as mortality and clinical functions, the negative association between MetS and HRQoL has been investigated in other countries (15-18). Among the first efforts in this field the negative association between MetS and physical or mental HRQoL have been reported mainly in Western societies, including an obese Italian population (19), an elderly Brazilian community (20) and postmenopausal Ecuadorian women (21). Considering the fact that, quality of life takes on dif-

ferent meanings based on the area and culture of population, there was a need to investigate the association between MetS and HRQoL in non-Western countries. To the best of our knowledge, findings of the TLGS provide the first evidence regarding this relationship in an urban Middle Eastern population (22). In this report, a summary of the TLGS findings regarding the association between MetS and HRQoL and its influential factors has been provided.

2. Evidence Acquisition

TLGS data collected between 2005 - 2007, was used to assess different aspects of the associations between MetS and HRQoL. Participants were adults aged $\geq$ 20 y, who were diagnosed without diabetes type 2 and had complete socio-demographic, clinical and HRQoL data (Figure 1). To assess HRQoL, we used the Iranian version of the short form health survey (SF-36), which has been validated in Iran (23); this widely used questionnaire contains 36 questions summarized into eight subscales, i.e four physical health related subscales including physical functioning, role limitations due to physical health problems, bodily pain, general health and four mental health-related subscales including vitality, social functioning, role limitations due to emotional problems, and mental health. The physical subscales constitute: (1) the physical component summary (PCS) and (2) the four mental subscales are termed as the mental component summary (MCS) (24). The score attributed to each subscale ranges from 0 to 100 as the worst and the best conditions of health respectively. Calculation of the PCS and MCS scores was done using the Quality Metric Health Outcomes Scoring software (25). The most common MetS definitions applied in the TLGS reports have been categorized in two, the insulin resistance-based- (26-28) and the waist circumference-based definitions (29-32).

3. Results

Mean age of participants was 46.5 $\pm$ 14.4 years and 64.3% of participants were female. There were significant differences in demographic and clinical characteristics between individuals with and without metabolic syndrome in both genders, except for fasting blood sugar, physical activity and smoking for women and except educational level, fasting blood sugar, physical activity and smoking and medication users in men. The findings of the association between MetS and HRQoL are presented in three main themes including: (1) the effect of gender, (2) the nature and duration of MetS and (3) the effect of definitions and measurements.

3.1. The Effect of Gender

At first glance, comparing HRQoL between those with (n = 361) and without MetS (n = 589), our results showed significant differences in all HRQoL domains except for the vitality (P = 0.1) and role emotional (P = 0.06) sub-scales. After adjustment, these differences were observed only in women and not in men in all subscales (P < 0.05), except for role physical, vitality, social functioning, role emotional and MCS (Figure 2). In this regard a sex specific logistic analysis revealed MetS as a determinant of poor physical HRQoL only in women (OR: 1.78; 95% CI: 1.21 - 2.61). In addition in women, with increase in the number of Met.S components a significant decreasing trend in the PCS was observed (P < 0.001) (22).

Considering our previous findings, regarding impairment of HRQoL in the physical aspect only in women, but not in men, and the lack of evidence on the related underlying mechanism of this gender difference, menopause was hypothesized to be a potential influential factor. Hence, the association between MetS and HRQoL was further investigated in two different durations of women, including the reproductive and post-menopausal periods; the study population included 603 women, of whom 432 women were reproductive aged and the remaining were of the post-menopausal age (n = 171); findings indicated that in both groups of women, the components of MetS, including WC, TG, blood pressure and FBS were significantly higher and HDL was significantly lower than those without MetS. Comparison of HRQoL subscale scores indicated that HRQoL scores in PCS and physical subscales including physical functioning, role physical and general health were significantly lower in women of reproductive age compared to their counterparts without MetS. Neither MCS nor mental subscales scores were significantly different in both groups of women of reproductive age. In post-menopausal women, only the bodily pain subscale score was significantly higher in women without MetS compared to women with MetS. Poor HRQoL is defined as PCS and MCS scores below mean scores. In reproductive age women, ORs for poor PCS were significantly higher in those with MetS, compared to women without Mets after adjusting for age (OR: 1.7, 95% CI: 1.0 - 3.0; P < 0.05). However, ORs for MCS were not significantly different in women with and without Mets. In addition, in post-menopausal women, ORs of poor MCS and PCS did not differ significantly in women with and without MetS. To summarize, findings indicated that MetS was associated with poor HRQoL only in women of reproductive age and only in the physical aspect (19).

Previous findings of TLGS indicate that the impair-

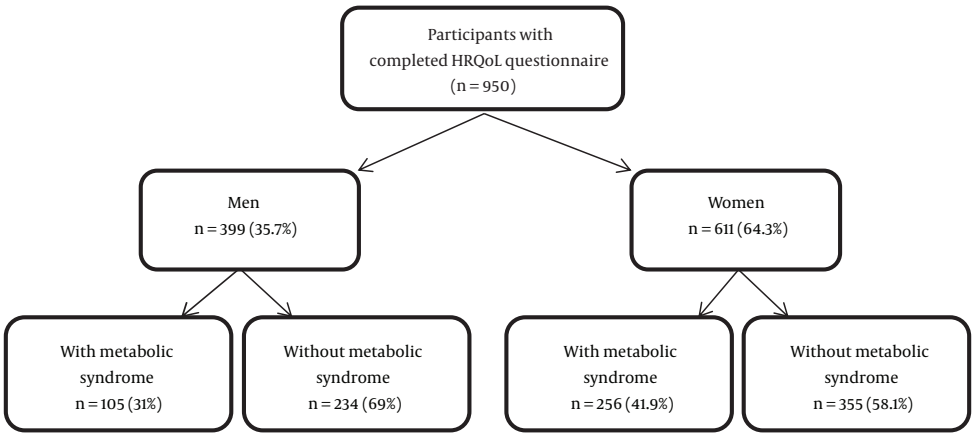

Figure 1. The sampling frame of study. Abbreviation: HRQoL, health-related quality of life.

ment of HRQoL in those with MetS was observed mainly in women but not in men; therefore, potential influential factors responsible for gender differences in the association between MetS and HRQoL were further assessed. For this purpose, the structural equation modeling (SEM) approach was used, and findings indicated that the most physical subscales impaired by MetS in women were bodily pain and physical functioning. In addition, physical activity in both genders, age and education only in women and smoking only in men were factors directly associated with physical aspects of HRQoL. Marital status and physical activity in women and age in men were factors directly associated with mental aspects of HRQoL. Moreover, different structures of MetS and physical HRQoL constructs in men and women as well as age and smoking with significant gender-specific effects on mental HRQoL were factors responsible for gender specific pattern observed (21).

3.2. The Effect of Nature and Duration of MetS

Furthermore, the next question that arose in this regard was whether or not persistence of MetS has any influence on HRQoL. To answer this question, participants of the TLGS who had participated in all three phases of the study (n = 643) were categorized into four groups including (1) those without MetS in all three phases, (2) those with MetS in just one phase (transient) (3) those with MetS for two consecutive or intermittent phases (intermittent) and (4) those with MetS for all three phases and their HRQoL scores were then compared. The findings showed that after adjusting for confounding variables, the HRQoL scores in PCS, bodily pain and general health subscales differed significantly only in women of the mentioned study groups. However, for men, no significant differences were observed in HRQoL scores of four study groups. In the adjusted models, only women with intermittent MetS indicated higher risk for reporting poor PCS (OR: 2.75, 95% CI: 1.19 - 6.37; $P < 0.001$), compared to women without MetS. Whereas, men with transient, intermittent and persistent MetS did not show any difference in risk for reporting poor PCS and MCS, compared to men without MetS (33).

Based on previous studies, since glucose tolerance status could associate with impaired HRQoL (34, 35); the association between MetS and HRQoL was further investigated in TLGS participants (n = 946) considering glucose regulation impairment as an important component of MetS. The findings indicated that in both groups of women with normal and impaired glucose regulation, physical HRQoL was impaired in those with MetS compared to those without the condition. However, in both groups of men with normal and impaired glucose regulation no significant difference was observed based on presence or absence of MetS in men. To conclude, MetS was associated with poor HRQoL in physical subscales in both groups of women with normal and impaired glucose regulation(36).

3.3. The Effect of Definitions and Measurements

There are a number of definitions for MetS including IR-based and WC-based definitions, because of which the diagnostic power of these definitions of MetS in detection of poor HRQoL may differ. Therefore, the diagnostic impact of different definitions of MetS in detection of poor HRQoL as subjective measurement of health was further investigated. First, MetS was defined using four different WC-based definitions of MetS including the National

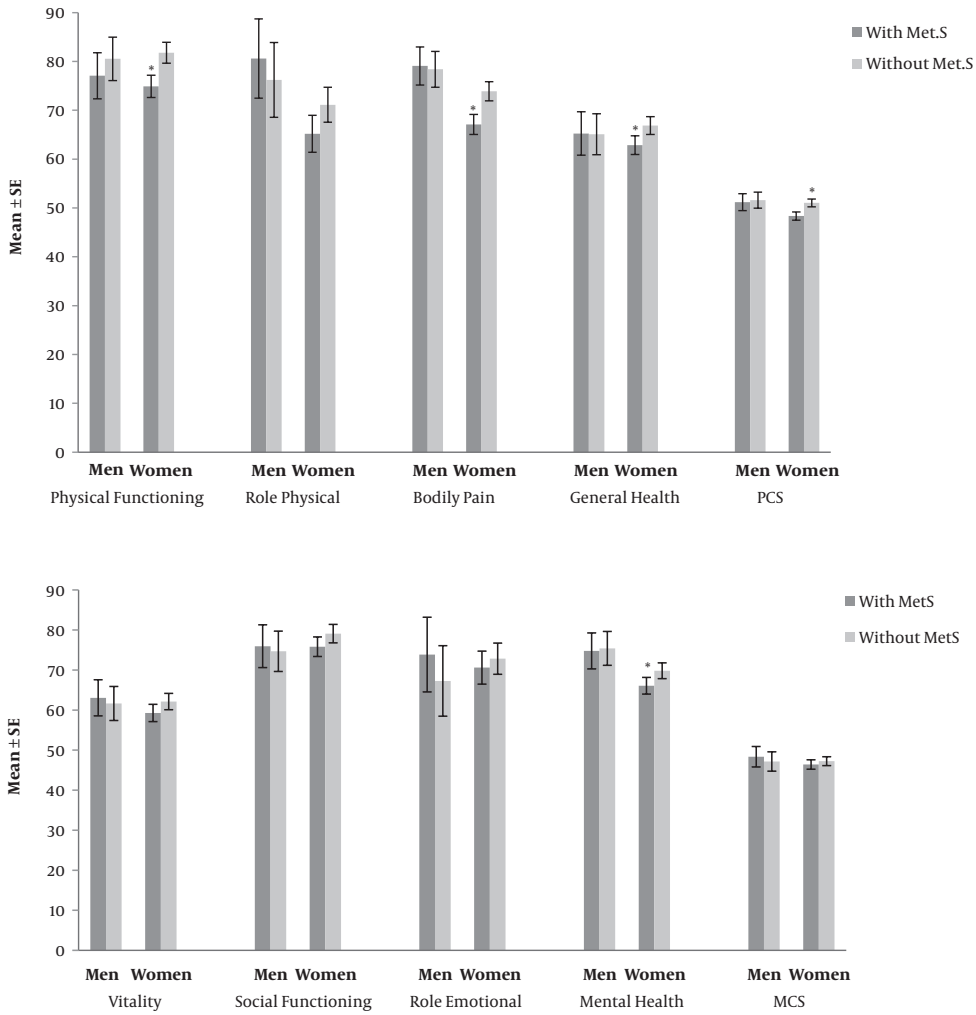

Figure 2. HRQoL physical and mental scores in men and women. Data are represented as mean ± SE. * P < 0.05. Abbreviations: MCS, mental component summary; MetS, metabolic syndrome; PCS, physical component summary.

Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), the International Diabetes Federation (IDF) and the Joint Interim Statement (JIS). The findings indicated that in women, the highest rate of MetS was detected using AHA/NHLBI (47.0%) followed by the JIS (44.2%), NCEP-ATP III (42.4%) and IDF (40.3%) definitions. Whereas in men, the highest rate of MetS was detected by the JIS (51.9%), followed by IDF (51.3%), AHA/NHLBI (36.9%) and NCEP-ATP III (32.4%). The HRQoL subscale scores, using different definitions are provided in Figure 3, as indicated, using all WC-based definitions, HRQoL scores were higher in men, compared to women. Poor HRQoL in physical and mental aspects were defined as the first tertile of PCS and MCS, respectively. Findings of logistic regression analysis indicated that ORs (95%CI) adjusted for age, physical activity, smoking, education and marital status for poor PCS using NCEP-ATP III, AHA/NHLBI, IDF and the JIS definitions were 1.20 (0.64 - 2.13), 1.20 (0.70 - 2.11), 1.0 (0.60 - 1.70) and 0.92 (0.53 - 1.60) in men and 1.70 (1.04 - 2.63), 1.51 (1.0 - 2.40), 1.92 (1.20 - 3.10) and 1.63 (1.02 - 2.60) in women respectively. In addition, adjusted ORs (95% CI) for MCS using NCEP-ATP III, AHA/NHLBI, IDF and JIS definitions were 0.82 (0.50 - 1.50), 0.90 (0.50 - 1.54), 1.30 (0.73 - 2.20) and 1.30 (0.73 - 2.20) in men and 1.20 (0.80 - 1.90), 1.0 (0.62 - 1.52), 0.90 (0.06 - 1.40) and 0.90 (0.60 - 1.40) in women respectively. In summary, all investigated definitions of MetS were similar in detection of poor physical and

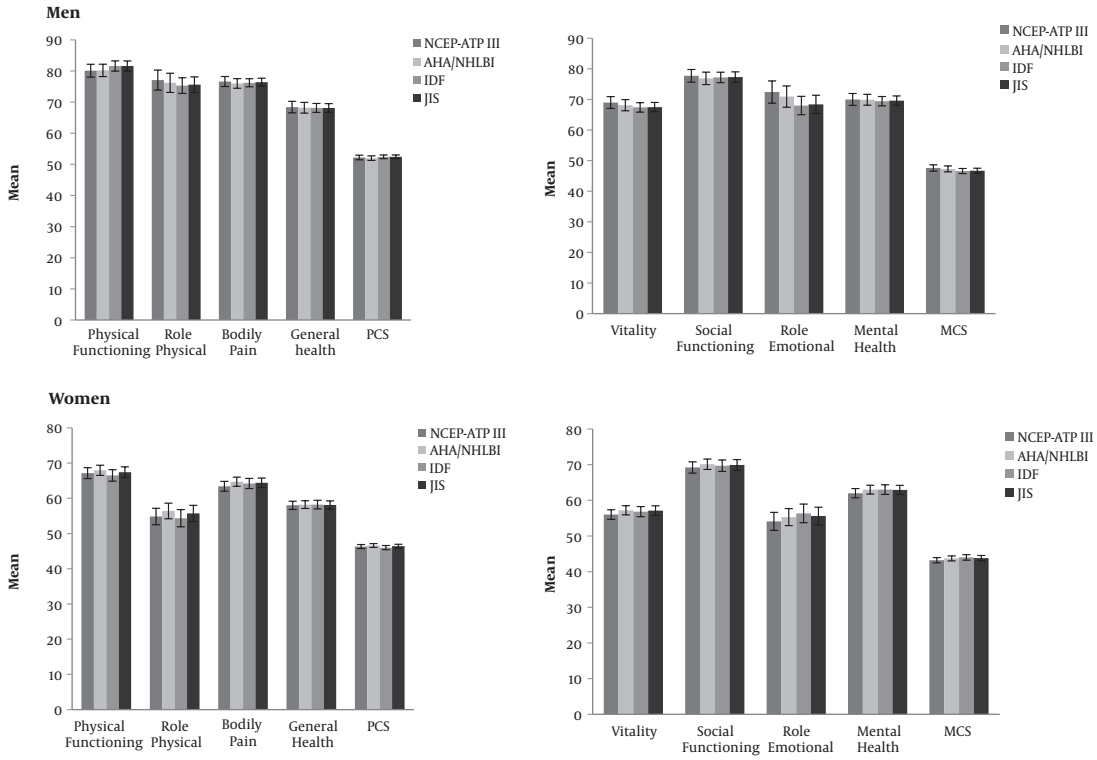

Figure 3. HRQoL scores according to different waist circumference-based definitions of metabolic syndrome in men and women. Data are represented as mean ± SE. AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; IDF, the International Diabetes Federation; JIS, the Joint Interim Statement; MCS, mental component summary; NCEP-ATP III, the National Cholesterol Education Program Adult Treatment Panel III; PCS, physical component summary.

mental HRQoL; furthermore, except for the AHA/NHLBI definition, all other definitions of MetS investigated significantly detected poor physical HRQoL, only in women (37).

Second, the diagnostic powers of different IR-based definitions of MetS including the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), and the American Association of Clinical Endocrinology (AACE) in detection of poor HRQoL were compared. In women, the highest rate of MetS was detected using the WHO definition (40.6%) followed by AACE (29.5%) and EGIR (25.5%). In men, the highest rate of MetS was detected by WHO (44.2%) followed by AACE (33.2%) and EGIR (25.8%); HRQoL subscale scores, using different IR-based definitions are presented in Figure 4, as it is indicated, using all definitions, most of HRQoL scores were higher in men compared to women. Findings of logistic regression analysis indicated that ORs (95%CI) adjusted for age, smoking, education, marital status and menopause in women for poor PCS using WHO, EGIR and AACE definitions were 1.72 (0.88 - 3.35), 1.80 (0.69 - 4.69) and 1.95 (0.84 - 4.53) in men and 0.96 (0.57 - 1.60), 0.93 (0.48 - 1.81) and 1.01 (0.55 - 1.85) in women respectively. Adjusted ORs (95% CI) for detection of poor MCS using WHO, EGIR and AACE definitions were 0.75 (0.37 - 1.49), 0.93 (0.38 - 2.23) and 0.97 (0.41 - 2.28) in men and 0.89 (0.55 - 1.45), 0.97 (0.54 - 1.74) and 1.00 (0.56 - 1.79) in women respectively. In conclusion, as OR (95% CI) values indicated, none of (IR)-base definitions could detect poor physical and mental HRQoL in either gender (20).

4. Discussion

In summary, the current findings revealed that the association between MetS and HRQoL followed a sex specific pattern which was mainly significant only in women and in the physical aspect. Some of the gender difference observed in the association between MetS and HRQoL was due to differences in the structures of both MetS and the physical aspect of HRQoL in men and women and also, sex specific effects of age and smoking on mental aspect of HRQoL. Furthermore, the significant association between MetS and poor physical HRQoL in women, was limited to women of reproductive age. Gender difference in the association between MetS and HRQoL has also been reported in previous studies, some of which showed this association

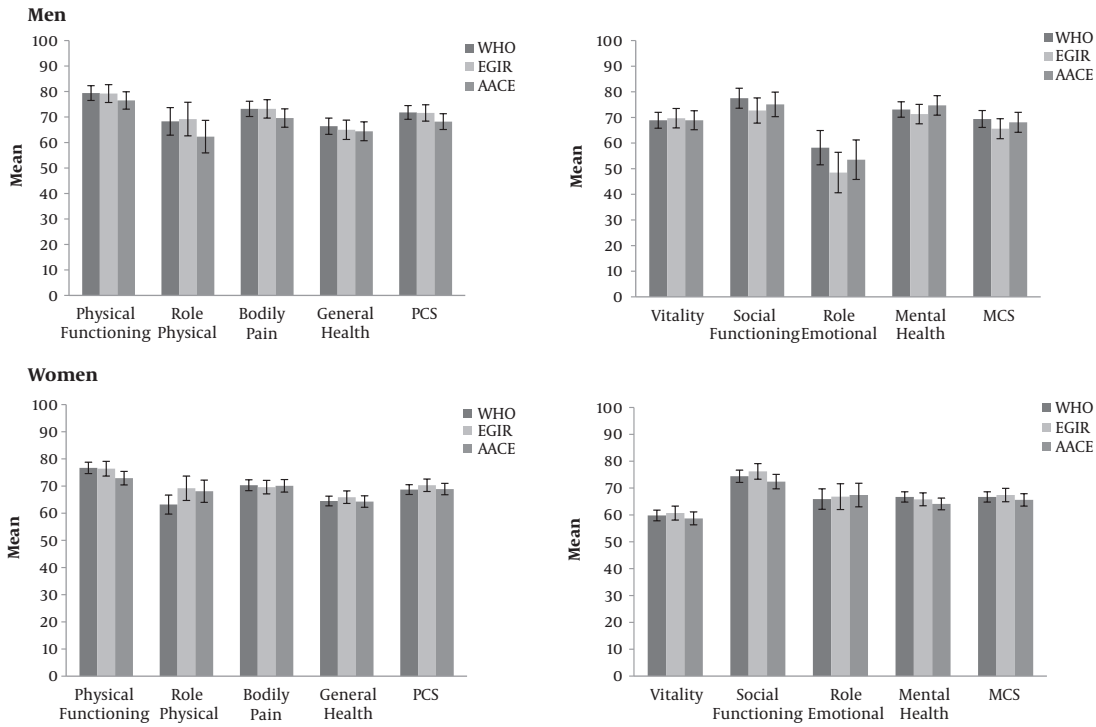

Figure 4. HRQoL scores according to different Insulin-based definitions of metabolic syndrome in men and women. Data represented as mean ± SE. Abbreviations: AACE, the American Association of Clinical Endocrinology; EGIR, the European Group for the Study of Insulin Resistance; MCS, mental component summary; PCS, physical component summary; WHO, the World Health Organization.

in women (15, 16) or in men (38). In addition, similar to TLGS findings, in some studies this relationship was significantly revealed only in the physical aspect (17, 39). However, other studies reported this association in mental (38) or both physical and mental aspects of HRQoL (40). Regarding the potential effects of duration and type of MetS components on the association between MetS and HRQoL, TLGS findings furthermore indicated that after considering both duration and presence of impaired glucose as an important component of MetS, the same gender specific pattern remained. In other words, irrespective of both duration of MetS and presence of impaired glucose regulation, this syndrome was still associated with poor physical HRQoL only in women. However, findings of another study in Finnish population, indicated that different glucose tolerance statuses were associated with impairment of HRQoL (35). In addition, in terms of using different definitions of MetS, findings indicated no significant gender differences in any of the applied WC-based and IR-based definitions of MetS in detection of poor physical and mental HRQoL. To the best of our knowledge, there is no similar study in this regard which has investigated the diagnostic value of different definitions of MetS in detection of poor HRQoL; based on our findings, while all WC-based MetS definitions detected poor physical HRQoL only in women with MetS, none of the IR-based MetS definitions could detect poor physical or mental HRQoL in either of genders.

The current review summarizes all TLGS findings regarding HRQoL which have been focused on MetS. This report could provide a comprehensive view regarding different aspects of the association between HRQoL and MetS in a Middle Eastern population. However, the cross-sectional nature of these studies, limits our ability to draw conclusions regarding the causal association between MetS and HRQoL. In addition not considering rural/sub-urban populations of Iran limits the generalizability of the current results. It is recommended that other possible confounders that could affect the present results, be considered in future research.

4.1. Conclusions

In the TLGS population, the association between MetS and HRQoL followed a sex specific pattern which was mainly significant only in women and in physical aspect.

To confirm these findings further studies on different urban and rural populations in Iran seem essential.

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The Nitrate-Nitrite-Nitric Oxide Pathway: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: We describe here the contributions of the Tehran lipid and glucose study (TLGS) to understanding different aspects of the nitrate (NO_3)-nitrite (NO_2)-nitric oxide (NO) pathway in health and disease.
Evidence Acquisition: All English-language documents from the TLGS, focused on NO pathway were searched using the PubMed, Scopus, and Embase databases.
Results: Reference values of serum concentrations of NO metabolites (nitrate+nitrite or NOx) were 11.5 - 76.4, 10.1 - 65.6, and 10.3 - 66.8 μmol/L in men, women, and the total population, respectively. Circulating NOx was affected by age, smoking habits, menopause status, thyroid hormones, and various pathologic conditions. Elevated serum NOx was related to increased incidence of metabolic syndrome (odds ratio (OR) = 1.75, 95% confidence interval (CI) = 1.19 - 2.59), hypertriglyceridemic-waist phenotype (OR = 1.39, 95% CI = 1.05 - 1.93), chronic kidney disease (OR = 1.86, 95% CI = 1.10 - 3.14) in women, and cardiovascular disease (hazard ratio (HR) = 1.35, 95% CI = 1.01 - 1.80] in the total population. In participants with low vitamin C intake, higher intakes of NO_2 ($\geq$ 8.77 mg/d) were accompanied with increased risk of diabetes (HR = 2.43, 95% CI = 1.45 - 4.05). A decreased risk of hypertension (OR = 0.58, 95% CI = 0.33 - 0.98) and chronic kidney disease (OR = 0.50, 95% CI = 0.24 - 0.89) was observed in response to higher intakes of NO_2.
Conclusions: Circulating NOx is associated with and could predict the risk of metabolic disorders in a general population. Moreover, dietary NO_3/NO_2 exposure from usual diets seems to contribute to development of noncommunicable diseases.

Keywords: Nitric Oxide, Nitrate, Nitrite, Diabetes, Obesity, Metabolic Syndrome, Cardiovascular Disease

1. Context

Nitric oxide (NO), a simple ubiquitous signaling molecule, is suggested to be linked with several physiological processes including regulation of vascular homeostasis and blood pressure, inhibition of platelet activation, regulation of energy and lipid metabolism, mitochondrial biogenesis, and the modification of various physiological pathways (1-3). Interrupted NO metabolism, including either reduced or elevated production of NO, as well as its decreased bioavailability, has been reported as a risk factor and/or prognostic biomarker for development of chronic disorders especially cardiovascular disease (CVD), renal dysfunction, diabetes, hypertension (HTN), and different types of cancer (4-9).

In this review, we aim to describe contributions of the Tehran lipid and glucose study (TLGS) to understanding different aspects of the nitrate (NO_3)-nitrite (NO_2)-nitric oxide (NO) pathway in health and disease. All English-language documents from the TLGS focusing on serum concentrations of NO metabolites (nitrate+nitrite or NOx), or dietary intake of NO_3/NO_2 were searched from PubMed, Scopus, and Embase databases. To summarize findings of these studies in the the first author's name, date of publication, number of participants, years of follow-up period in cohort studies, serum NOx concentrations (μmol/L), exposure levels of dietary NO_3 and NO_2, definition of outcomes, and odds ratios (ORs) or hazard ratios (HRs) with their corresponding 95% confidence intervals (95% CIs) were ex-

tracted.

1.1. NOx Measurement in TLGS

TLGS is an ongoing community-based prospective study being conducted to investigate and prevent non-communicable diseases (NCDs), in a representative sample in the district 13 of Tehran, the capital city of Iran (10).

In the third phase of TLGS (2006 - 2008), in a sub-sample of participants (n = 4407), serum NOx levels were measured by a rapid and simple spectrophotometric method, validated in our laboratory (11, 12). Inter- and intra-assay coefficients of variations of measurements were 5.2% and 4.4%, respectively; the sensitivity of the assay was 2.0 μmol/L and its recovery was 93% $\pm$ 1.5% (13).

The mean ($\pm$ SE) of serum NOx concentrations in normal subjects were 24.8 $\pm$ 0.02 and 24.4 $\pm$ 0.01 μmol/L in the TLGS men and women, respectively (14). In our adults, the reference values of serum NOx concentration were 11.5 - 76.4, 10.1 - 65.6, and 10.3 - 66.8 μmol/L in men, women, and total population, respectively (15). In the TLGS pediatric population (189 boys and 212 girls, aged 4 - 19 years), reference values for serum NOx concentrations were 13.6 - 69.2, 11.4 - 66.0, and 12.2 - 69.4 μmol/L in boys, girls, and total population, respectively (16).

1.2. Factors Affecting Circulating NOx

In our population, a higher NOx levels was observed in men, compared to women aged 20 - 29 years (25.1 $\pm$ 0.03 vs. 22.7 $\pm$ 0.02 μmol/L), and serum NOx concentration showed a peak at 50 - 59 years in both genders; increased NOx levels between 50 and 59 years of age, declined after 60 years in men but not in women (14). Overall, there was also a significant increasing trend in circulating NOx across age groups, only in women (14). Our study conducted on 1209 middle-aged (40 - 60 years) TLGS participants indicated higher serum NOx values in postmenopausal women (median = 29, IQR = 21 - 43 μmol/L), compared to women with regular cycles (25.5 μmol/L, IQR = 19 - 39) or men (26 μmol/L, IQR = 20 - 37) (17). Serum NOx levels also show considerable elevation across pre-menopause to post-menopause transition (18); in a conditional fixed-effect logistic regression model, the chance of "transition to menopause" and "menopause" increased by 2.44 (95% CI = 1.17 - 5.08) and 2.27 (95% CI = 1.23 - 4.18) per 1 standard deviation increase in circulating NOx levels (18).

In a cross-sectional analysis, conducted on 1974 adult participants of the Tehran thyroid study, serum NOx levels were negatively associated with free thyroxin (T_4) in men and anti-thyroperoxidase (TPO) levels in women (19). Insulin is another physiological factor that may affect serum NOx concentration. In our population, a higher circulating NOx was observed in the highest compared to the lowest quartile of fasting serum insulin, an association that was statistically significant only in women (28.5 vs. 25.4 μmol/L) (20). NOx concentration was also weakly correlated with a homeostatic model assessment of insulin resistance and quantitative insulin sensitivity check index in women (20).

Effects of life style factors, like dietary habits and smoking, as potential moderators of circulating NOx, have been less documented. The possible adverse effects of passive cigarette and water pipe (qalyan) smoking on serum NOx concentration were documented following the first report in 2010 from the TLGS data (21). Serum NOx was significantly higher in the healthy active smokers (28.9 vs. 24.1 μmol/L), compared to nonsmokers; the number of cigarette smoked was also positively correlated with serum NOx concentrations. Qalyan smokers had higher serum NOx levels, compared to the non-smoker controls (34.3 vs. 22.5 μmol/L); serum NOx values were comparable between passive smokers and non-smokers (21).

Alterations of circulating NOx in relation to dietary factors or eating behaviors seem to be a neglected area in the field of NO metabolism. In a cross-sectional analysis in the TLGS population, we found a significant positive association between L-arginine intake from usual diet and serum NOx concentrations (22); this association was affected by sex, age, body mass index (BMI) and HTN, and a greater association was observed in women, middle-aged and older adults, overweight and obese subjects, as well as non-hypertensive compared to hypertensive subjects (22). Regular dietary intakes of NO_3/NO_2 were correlated with their urinary excretion levels (r = 0.59, 95% CI = 0.49 - 0.67, and r = 0.29, 95% CI = 0.17 - 0.41, for NO_3 and NO_2, respectively) in a sub-sample analysis of our population; fasting serum NOx was not related to NO_3/NO_2 exposure (r = 0.19, 95% CI = 0.07, 0.32 and r = 0.09, 95% CI = -0.03, 0.23, for NO_3 and NO_2, respectively) (23).

Other potential factors affecting circulating NOx, like physical activity, have not been assessed in the setting of the TLGS.

2. Association Between NCDs and Circulating NOx

2.1. Obesity

Reports from a cross-sectional analysis, using the TLGS data by our group showed positive associations between serum NOx concentrations and anthropometric measures including BMI, waist circumference (WC) and waist to hip ratio (WHR) in women (13), results that remained only for

BMI > 30 kg/m^2 (β = 5.4, P = 0.001) in multivariable adjusted model (13). A significant trend of increasing serum NOx concentrations was also observed across categories of BMI in women (13). In a prospective approach, we reported that serum NOx, beyond being a probable indicator, may also be a novel predictor of obesity phenotypes. Following a median of 6.3 years study of 2243 adults, we observed an association between development of hypertriglyceridemic waist phenotype (HTW) and elevated baseline serum NOx in women (HR = 1.39, 95% CI = 1.05 - 1.93) (24) (Table 1); compared to women in the first tertile of serum NOx, those in the third tertile ($\geq$ 30.9 vs. < 19.9 μmol/L) had higher WC, both at baseline and follow-up examinations (24). We also showed that circulating NOx could predict changes of lipid accumulation product (LAP) index, a novel biomarker of central lipid accumulation related to risk of diabetes and CVD (25); serum NOx in the highest tertile was positively related to 6-years LAP changes (β = 5.23, 95% CI = 1.69 - 7.78) (25).

2.2. Dysglycemia and Diabetes

In an earlier study in the TLGS population, we observed higher serum NOx values in diabetic subjects compared to their corresponding controls (34.6 μmol/L, 95% CI = 31.3 - 38.2 vs. 30.2 μmol/L, 95% CI = 27.9 - 32.6) (29).

The first investigation addressing potential association of serum NOx and diabetes was conducted on the TLGS population (15); a remarkable result to emerge from this cross-sectional analysis was that circulating NOx above reference values (65.6 μmol/L) increased chances of having type 2 diabetes in women (OR = 1.67, 95% CI = 1.10 - 2.55) (15).

2.3. Hypertension, Chronic Kidney Disease, and Cardiovascular Events

Limited number of studies have investigated NO-blood pressure relationship in the framework of a population-based setting. In the TLGS population, compared to controls, serum NOx levels were higher in both men and women with stage 1 HTN (14% and 23%, respectively); conversely, circulating NOx was significantly reduced in men with stage 2 HTN (30). In both stages, treated-hypertensive men had a higher serum NOx concentration, whereas in women, increased circulating NOx was observed just in stage 1 HTN (30). Considering serum NOx as an independent variable in the analysis, we observed that elevated serum NOx was not related to chances of having HTN (OR = 0.91, 95% CI = 0.49 - 1.70, and OR = 1.38, 95% CI = 0.95 - 2.01, in men and women, respectively) (15).

In a cross-sectional setting of 3462 TLGS participants, the odds of having chronic kidney disease (CKD) in both men and women, in the highest compared to the lowest tertile of serum NOx ($\geq$ 32 vs. < 21 μmol/L), were significantly higher (OR = 1.61, 95% CI = 1.05 - 2.64 and OR = 2.64, 95% CI = 1.91 - 3.66); following adjustment for diabetes, CVD, HTN, medications and triglycerides (TG)-to-high density lipoprotein-cholesterol (HDL-C) ratio, elevated serum NOx was related to the likelihoods of CKD only in women (OR = 2.48, 95% CI = 1.76 - 3.49) (27) (Table 1). Our prospective design within the TLGS indicated that, in the presence of the well-known risk factors, serum NOx values $\geq$ 32 μmol/L may predict 3-year risk of CKD in women (OR = 1.86, 95% CI = 1.10 - 3.14) (27). In a 3-year follow-up of adult (aged $\geq$ 30 years) men and women participated in the third phase of TLGS, results indicated that compared to the lowest quartiles of serum NOx, the incidence of CVD (10.1 vs. 4.4%, P = 0.002) was higher in the highest quartile and the risk of CVD events increased by 35% (HR = 1.35, 95% CI = 1.01 - 1.80) for each 1 unit of increase in Ln-transformed serum NOx concentrations (28) (Table 1); in this analysis, incorporating circulating NOx into the traditional CVD risk model appropriately reclassified over 6% of individuals at risk (28).

2.4. Metabolic Syndrome

Only a few population-based studies have documented the importance of circulating NOx as a novel biomarker of MetS. In a study of 851 children and adolescents, aged 4 - 19 years, a higher prevalence of MetS (13.2% vs. 6.1%) was observed in the highest compared to the lowest quartile of serum NOx concentrations ($\geq$ 33.0 vs. < 19.0 μmol/L) (31); age-and sex adjusted odds ratio of having MetS was significantly higher in the subjects with highest levels of NOx (OR = 2.2, 95% CI = 1.1 - 4.7) (31). Furthermore, co-clustering of NOx with other MetS components indicated that circulating NOx can be considered as a component of MetS (31).

In a short-term follow-up of the TLGS participants, risk of developing MetS was significantly higher (OR = 1.75, 95% CI = 1.19 - 2.59) in women who had higher basal serum NOx values ($\geq$ 35 μmol/L) (26) (Table 1); serum NOx-to-creatinine ratio, a marker of endogenous NO production, was also related to developing MetS in women (26).

3. Dietary Intake of NO_3 and NO_2 in Relation to Cardio-Metabolic-Renal Disease

Considering the importance of NO_3/NO_2 exposure in NO homeostasis and its possible role in pathogenesis of NCDs, we recently developed a comprehensive database of the NO_3/NO_2 content of commonly consumed food items (32). Following estimation of NO_3/NO_2 exposure from usual diet in the TLGS population, we reported, for the first

Table 1. Associations Between Serum NOx Levels and the Incidence of Non-Communicable Diseases in the TLGS Population

Author	Study Population	Years of Follow-Up	Outcomes	Levels of Serum NOx (μmol/L)	Adjusted OR (95% CI) or HR (95% CI)
Ghasemi et al. (26)	Adult men (n = 644)	3.3	Metabolic syndrome	$\leq$ 75th percentile	1.00
				> 75th percentile	0.93 (0.58 - 1.49)[a]
	Adult women (n = 1137)	3.3	Metabolic syndrome	$\leq$ 35.0	1.00
				> 35.0	1.75 (1.19 - 2.59)[a]
Bahadoran et al. (27)	Adult men (n = 1063)	3	Chronic kidney disease	< 21.0	1.00
				21.0 - 32.0	1.44 (0.67 - 3.11)[a]
				$\geq$ 32.0	0.98 (0.44 - 2.20)[a]
	Adult women (n = 1441)	3	Chronic kidney disease	< 21.0	1.00
				21.0 - 32.0	1.53 (0.89 - 2.63)[a]
				$\geq$ 32.0	1.86 (1.10 - 3.14)[a]
Hadaegh et al. (28)	Adult men and women (n = 2443)	3.1	Cardiovascular events	Ln-transformed NOx as a continuous variable	1.35 (1.01 - 1.80)[b]
Bahadoran et al. (24)	Adult men (n = 762)	6	Hypertriglyceridemic-waist phenotype	< 20.9	1.00
				20.9 - 29.9	1.41 (0.95 - 2.07)[a]
				$\geq$ 29.9	1.16 (0.78 - 1.72)[a]
	Adult women (n = 1172)	6	Hypertriglyceridemic-waist phenotype	< 19.9	1.00
				19.9 - 30.9	1.19 (0.86 - 1.64)[a]
				$\geq$ 30.9	1.39 (1.05 - 1.93)[a]

Abbreviations: HR, hazard ratio; NOx, nitric oxide metabolites (nitrate+nitrite); OR, odds ratio.
[a] Indicates OR.
[b] Indicates HR.

time, the hazards of diabetes, HTN, CKD and CVD in response to different levels of dietary NO_3/NO_2 (Table 2). Our findings indicate that incidence of diabetes was increased (HR = 2.43, 95% CI = 1.45 - 4.05, HR = 1.88, 95% CI = 1.12 - 3.15, respectively) in participants with low-vitamin C diets and higher intakes of total ($\geq$ 8.77 mg/d) and animal-based ($\geq$ 3.24 mg/d) NO_2; we found no significant association between NO_3 in overall, and plant- or animal sources and the risk of diabetes (33). The highest compared to the lowest NO_2 intake ($\geq$ 10.7 vs. < 7.6 mg/d) was accompanied with a significant reduced risk of HTN (OR = 0.58, 95% CI = 0.33 - 0.98) and CKD (OR = 0.50, 95% CI = 0.24 - 0.89) (34). We also observed that in subjects with lower dietary total antioxidant capacity (TAC), higher intakes of NO_3 ($\geq$ 430 mg/d) were accompanied with an increased risk of CVD (HR = 3.28, 95% CI = 1.54 - 6.99); no evidence was documented in relation to NO_2 and the occurrence of CVD events during 6.7 years of follow-up (35).

4. Conclusions

Our observations imply that NO may play an independent role in predicting the CVD, CKD and obesity phenotypes, beyond the known classical indices. Higher NO_2 exposure alongside with a low-vitamin C intake may increase the risk of diabetes whereas high-NO_3 diet may decrease the risk of HTN and CKD. Furthermore, higher NO_2 intakes in the context of low-TAC diet contributes to development of CVD events. In our view, these findings make a major contribution towards enhancing current understanding of potential health outcomes in response to long-term exposure of NO_3/NO_2.

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Table 2. Association Between Dietary Intakes of NO_3 and NO_2 and the Incidence of Non-Communicable Diseases in the TLGS Population

Author	Study Population	Years of Follow-Up	Outcomes	Levels of Dietary Intakes of NO_3 or NO_2	Adjusted OR (95% CI) or HR (95% CI)
Bahadoran et al. (33)	Adult men and women (n = 2139)	5.8	T2DM	> 410 mg/d NO_3	1.38 (0.90 - 2.11)[a]
	Adult men and women (n = 2139)	5.8	T2DM	> 8.77 mg/d NO_2 alongside with a low-vitamin C diet	2.43 (1.45 - 4.05)[a]
	Adult men and women (n = 2139)	5.8	T2DM	> 8.77 mg/d NO_2 alongside with a high-vitamin C diet	0.91 (0.47 - 1.73)[a]
Bahadoran et al. (34)	Adult men and women (n = 1780)	5.8	CKD	< 365 mg/d NO_3	1.00
				365 - 510 mg/d NO_3	1.04 (0.68 - 1.57)[b]
				≥ 510 mg/d NO_3	0.76 (0.43 - 1.24)[b]
	Adult men and women (n = 1780)	5.8	CKD	< 7.6 mg/d NO_2	1.00
				7.6 - 10.7 mg/d NO_2	0.76 (0.50 - 1.13)[b]
				≥ 10.7 mg/d NO_2	0.50 (0.24 - 0.89)[b]
	Adult men and women (n = 1878)	5.8	HTN	< 359 mg/d NO_3	1.00
				259 - 505 mg/d NO_3	1.02 (0.68 - 1.51)[b]
				≥ 505 mg/d NO_3	0.81 (0.48 - 1.38)[b]
	Adult men and women (n = 1878)	5.8	HTN	< 7.5 mg/d NO_2	1.00
				7.5 - 10.6 mg/d NO_2	0.66 (0.44 - 1.00)[b]
				≥ 10.6 mg/d NO_2	0.58 (0.33 - 0.98)[b]
Bahadoran et al. (35)	Adult men and women (n = 2369)	6.7	CVD	≥ 430 mg/d NO_3 alongside with a high-TAC diet	1.10 (0.46 - 2.61)[a]
				≥ 8.9 mg/d NO_2 alongside with a high-TAC diet	1.10 (0.46 - 2.61)[a]
	Adult men and women (n = 2369)	6.7	CVD	≥ 430 mg/d NO_3 alongside with a low-TAC diet	3.28 (1.54 - 6.99)[a]
				≥ 8.9 mg/d NO_2 alongside with a low-TAC diet	2.14 (0.84 - 5.45)[a]

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; HTN, hypertension; NO_2, nitrite, NO_3, nitrate; OR, odds ratio; T2DM, type 2 diabetes; TAC, total antioxidant capacity.
[a] Indicates HR.
[b] Indicates OR.

Footnotes

Authors' Contribution: The study was designed and implemented by Zahra Bahadoran and Asghar Ghasemi. Zahra Bahadoran, Sajad Jeddi, Parvin Mirmiran, Amir Abbas Momenan, Fereidoun Azizi and Asghar Ghasemi prepared the manuscript. Asghar Ghasemi revised and supervised overall project. All authors read and approved the final version of manuscript.

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Outcomes of a Longitudinal Population-based Cohort Study and Pragmatic Community Trial: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: The Tehran lipid and glucose study (TLGS) is one of the oldest population-based longitudinal cohort studies, providing knowledge about the incidence and risk factors of some non-communicable diseases (NCDs) in West Asia which hitherto was relatively scarce. We reviewed the methods and results related to the outcome measurements of this study.
Evidence Acquisition: We reviewed all the TLGS papers which reported the incidence of NCDs.
Results: The TLGS was initiated in 1999 - 2001 on a population in district no. 13 of Tehran with the same age distribution of the overall Tehran population and with a middle socioeconomic status. Totally, 15005 individuals, aged $\geq$ 3 years, participated in the first examination; reexaminations were conducted in a triennial manner and 3550 individuals were added in the second examination. All participants were also followed up annually and asked about any medical event leading to hospitalization or death. A part of participants was assigned to an educational program for lifestyle modification. High incidence of cardiovascular disease (CVD), premature CVD, diabetes and hypertension (around 19, 6, 10 and 31 in men and 11, 5, 11 and 29 in women per 1000 person-year, respectively) besides the high incidence of pre-diabetes and pre-hypertension (around 46 and 76 in men and 37 and 49 in women per 1000 person-year, respectively) showed a worrying situation. Fortunately, the results of the community interventions were promising with around 20% reduction in the risk of metabolic syndrome up to six years.
Conclusions: These precise detections of different outcomes in the TLGS provided valuable evidences for prediction and prevention of NCDs in Iran with some novelties in the middle-income countries in the world. The Tehran thyroid study (TTS) and the Tehran cardiometabolic genetic study (TCGS), conducted in the framework of the TLGS, are among few studies aiming to determine the natural course of thyroid function and to identify patterns of genetic polymorphisms related to cardiometabolic outcomes, respectively.

Keywords: TLGS, Non-Communicable Disease, Risk Factors

1. Context

Cohort studies are used to determine the incidence of some defined outcomes, identify their risk and prognostic factors, assess the natural history of the disease and verify the impact of pragmatic interventions. The main strength of the cohort design for epidemiologic studies is that there is little doubt about the temporal relation between the exposures and the outcomes which are under study. Identification and classification of outcomes in cohort studies is a complex and challenging issue. Well-defined, -detected, and -classified outcomes are of characteristics of a well-established cohort study (1, 2).

Cohort studies have the capacity to evaluate multiple and different outcomes; however, this capacity is more substantial in longitudinal compared to life-table designs. The life-table design summarizes the effect of baseline exposures on the outcome over a period of time, whereas, the longitudinal design, which is potentially more expensive and complex, considers the time dependence of exposures and outcomes to address individual heterogeneity, changes during the time, and transitions between states of health and disease (3). Although population-based longitudinal cohort studies were established in western coun-

tries decades ago, numbers of such studies are rare and limited in low- and middle-income regions. The Tehran lipid and glucose study (TLGS) is one such a study, providing knowledge about the incidence and risk factors of some non-communicable diseases (NCDs) in West Asia which hitherto was relatively scarce (4). A part of this study has been dedicated to education for lifestyle modification, making the TLGS a pragmatic community trial (5). In this paper we will review the results from the TLGS regarding the incidence of some NCDs outcomes and the effect of educational interventions on some of these outcomes.

2. Evidence Acquisition

Among 580 papers published in English and 289 in Persian, up to March 2018, we only focused on papers which directly addressed the incidence of NCDs including cardiovascular disease (CVD), coronary heart disease (CHD), stroke, type 2 diabetes, pre-diabetes, hypertension, pre-hypertension, metabolic syndrome, chronic kidney disease, thyroid disorders, CVD-mortality and all-cause mortality. We also reviewed papers which reported the effect of educational interventions on cardiometabolic outcomes. Furthermore, as examples, we included some studies concerning the trend and change of cardiometabolic disorders during the follow-up in the TLGS.

3. Results

3.1. A Summary of the Methods

3.1.1. Study Population and Examinations

The first phase of the TLGS was initiated in 1999 - 2001 on a population under the coverage of three health centers in district no. 13 of Tehran. Totally, 15005 individuals, aged $\geq$ 3 years, participated in the first examination (response rate: 57.5%) (4). Reexaminations were conducted in a triennial manner and 3550 individuals were added in the second examination (Figure 1). To complete the pedigree of families, newborn children were added to the study population after they completed three years of age during the follow-ups. After completing baseline measurements (phase 1), participants under the coverage of one of the three health centers were assigned to an educational program for life style modification as a pragmatic community trial (5). Details of methods of sampling and measurements used at each examination, including demographics, medical and drug history, family history, physical exam, ECG, physical activity, nutrition and lab measurements, have been published before (4, 5). Many of the protocols have been based on the WHO and MONICA protocols for population surveys (4, 6).

3.2. Outcome Measurements

Besides the triennial reexaminations during in-person visits, all participants were followed up annually by telephone call to them or their family and asked about any medical event leading to hospitalization during the past year (Figure 1). In case of positive responses, related data were collected by a trained physician using hospital records or, if needed, a home visit. Moreover, in the case of mortality outside the hospital, data were collected from the death certificate, the report of forensic medicine and if needed a verbal autopsy from witnesses. All documents collected were reviewed by an adjudication committee and the final diagnosis was recorded, using a predefined coding protocol. The committee consisted of the physician who collected the data, an internist, an epidemiologist, a cardiologist, an endocrinologist, and other experts invited as needed. Response rate for follow-up was approximately 55 - 75 percent for in-person visits during different reexaminations and around 80 - 90 percent in annual telephone call follow-ups.

3.3. Educational Intervention

Interventions for lifestyle modification were carried out through primary prevention for cardio-metabolic disorders by improving dietary patterns, increasing physical activity, and encouraging smoking cessation. Primary educational interventions were classified in three categories, family-based, school-based and community-based interventions. The design of the TLGS for lifestyle interventions has been described previously (5); large and well-known interventional studies such as the North Karelia project and an international controlled trial in the multifactorial prevention of coronary heart disease and the American Heart Association guidelines were used in designing the intervention programs (7, 8). Table 1 shows a summary of interventions implemented up to the fourth triennial examination of the TLGS.

3.4. A Summary of the Outcome Results

Table 2 shows a review of the incidence of NCDs and related risk factors reported in the TLGS during 15 years of follow-up for men and women separately. For the outcomes of death and hospitalized events including cardiovascular diseases, the results were obtained by annual phone call follow-ups, confirmed by the adjudication committee. For other outcomes comprising diabetes, hypertension, metabolic syndrome and chronic kidney disease, the incidence are results of triennial in-person visits determined by drug history and/or confirmed by physical exam and lab measurements; details of methods have been provided for each outcome in its own specific paper, in

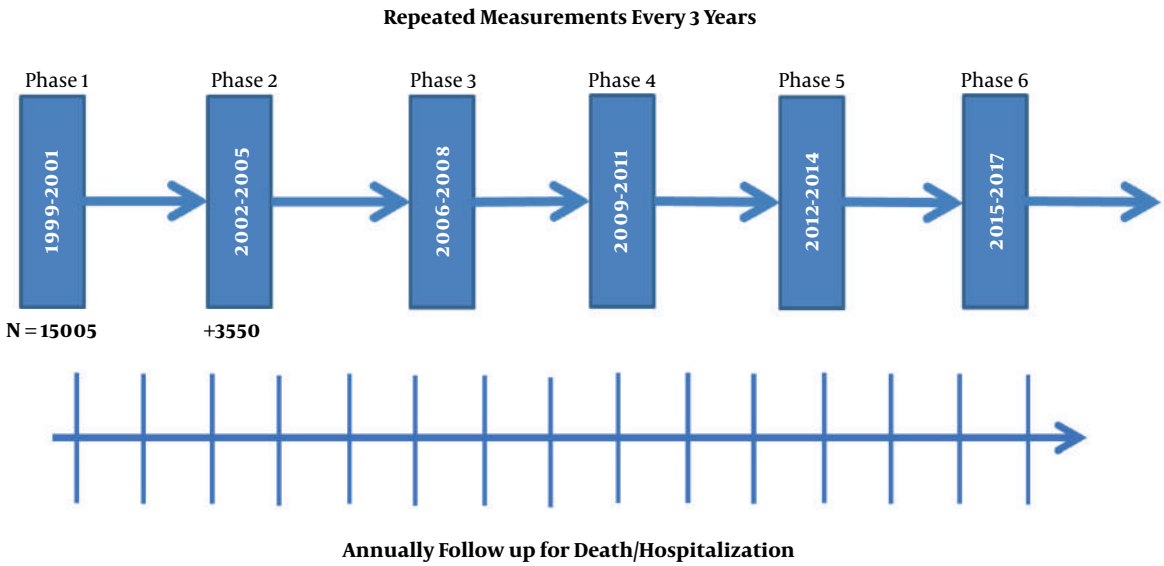

Figure 1. Follow-up in the TLGS including triennial reexaminations during in-person visits and annual telephone calls for death and hospitalization.

Table 1. A Summary of Lifestyle Education Programs: Tehran Lipid and Glucose Study

Intervention		Method of Delivery	Providers	Compliance
Family-based programs	Educational sessions	A 2-hour session with video and slide presentation and face-to-face consultation held with an average of 12 participants including family members, especially mothers, between baseline and 1st reexamination. Contents were mainly about healthy food preparation and nutritional values, benefits of physical activity, and harms of smoking.	Dieticians, general practitioners	About 50% of participants (70% of which were women) participated in the educational sessions
	Publications	"Courier of Health", published every 3 months, containing health-related topics (e.g. diet, nutrition, physical activity, smoking). Pamphlets, booklets and brochures (e.g. stress management techniques for students and parents).	Delivered by "health liaison"	Delivered to about 50% of households
Community-based programs	Educating key persons	Educating socially significant figures (law enforcers, clergymen etc.).	Dieticians, general practitioners, cardiologist and diabetologist	More than 80% of the households participated in at least one of public gatherings for national or religious holidays between each two examinations
	Public and group meetings	Providing health-related lectures during religious ceremonies (including Ramadan), 2 - 4 events annually. Conducting large-attendance seminars with the aim of presenting healthy lifestyles, 2 - 4 conferences annually.		
School-based programs	Classroom curriculum	"Living tobacco-free" intervention program. Educational classes for students	Dieticians and trained teachers	Nearly 70% of the school-based intervention program was successfully implemented
	Peer education	Forming school "health team" by students with the aim of peer education	Peer trained educator	
	Anti-smoking policies	Smoking prohibition for all the schoolchildren, teachers and employees inside the school	School supervisor	
	General policies	Labeling snacks, sold at school's shop regarding their healthiness. Educating school principals and volunteer teachers for lifestyle modification. Educational sessions for parents regarding healthy lifestyle	Dieticians	

which the predictors of related outcomes have also been explored (9-20). Appropriate follow-up time and detecting various outcomes enabled us to work on clinical prediction models regarding different cardiometabolic outcomes, CVD and diabetes in particular (15, 21-26). Future projects on validating, updating and developing new pre-

diction models for using in health care services in national level is ongoing. Pooling data from the TLGS with other large population-based cohort studies in the Iran Cohort Consortium (www.irancohorts.ir) will be resulted in more comprehensive information and research projects in this regard (27).

Since the TLGS is a longitudinal cohort with repeated measurements for exposures, it gave us the opportunity to investigate the effect of changes of risk factors on outcomes. For instance, we demonstrated that the three-year increase in systolic and diastolic blood pressure were associated with increased risk of CVD independently (29); or this rise in fasting plasma glucose could help identify high risk populations for incident type 2 diabetes, independent of important traditional risk factors (30). We also showed the effect of changes in anthropometric measures on the incidence of diabetes, CVD and total mortality (23, 31, 32). On other occasions, we studied the variability or trend of risk factors, by unravelling age effect and period effect, and in addition, the effect of some risk factors in childhood or adolescence on outcomes in adulthood (33-36).

Finally, the effect of educational interventions for life style modification on the outcomes of diabetes, metabolic syndrome and its components have been investigated in both short-and long-term periods. After 3 years, life style modification in the intervention group decreased the incidence of diabetes by at least 30%, compared to the control (37). The intervention could prevent the incidence of pre-diabetes in men by around 20% (14). The effect of intervention on decreasing the incidence of metabolic syndrome, as a cluster of NCDs risk factors, lasted up to 3 - 6 years by reducing the incidence by 20%. The effect of intervention was more prominent in the reduction of lipids and glucose, than in other components of metabolic syndrome (38).

4. Conclusions

The TLGS is a much-cited longitudinal population-based cohort study with fascinating results regarding the incidence of NCDs and their related risk factors. It is also a pragmatic community trial which showed the effectiveness of some educational interventions in a middle-income country.

The results of the TLGS show a higher risk of NCDs in our population in comparison to Western and Asia-Pacific countries. For instance, the incidence rate of CHD and diabetes in Tehran is around one percent per year. This rate for incidence of hypertension is around three percent per year. Total CHD incidence in our population is comparable to that of the US in the seventies and much higher than that in China with around 1 - 2 events per 1000 person-years (11). The high incidence of pre-diabetes and pre-hypertension of around four and six percent per year respectively, indicates a peak of diabetes and hypertension incidence in near future if we do not improve our primary health care system.

Since the TLGS follows a population with a wide age range, in future follow-ups, we will be able to investigate the trajectory of risk factors and diseases from childhood to adulthood. Furthermore, more follow-up will provide the opportunity to study NCDs with longer latent periods like cancers. Although our annual follow-up rate of 80% - 90% for hospitalizations and death events in the giant metropolis of Tehran seems fascinating, we need to try and improve the triennial follow-up rates for in-person visits. The Tehran thyroid study (TTS) and the Tehran cardiometabolic genetic study (TCGS) have conducted in the framework of the TLGS. TTS aims to evaluate the prevalence, incidence and natural course of thyroid diseases and their long-term consequences in terms of cardiometabolic disorders and all-cause mortality (39). TCGS seeks to identify relevant patterns of genetic polymorphisms related to cardiometabolic risk factors which will allow exploration of gene-gene and gene-environment interactions regarding NCD outcomes (40). Nevertheless, new measurements for detecting intermediate outcomes like intima media thickness, aorta velocity, DXA and MRI as well as biomarkers can widen our research horizons.

Although the TLGS gives us an opportunity to detect the effect of community education on lifestyle modification in a real world, randomization in such a population-based community trial is difficult and is considered as a limitation for our interventions. Lost to follow-up and crossing between participants in intervention and control areas are other limitations of the TLGS. Appropriate epidemiological and statistical methods, such as using different statistical models, propensity score and inverse probability weighting for non-respondents, considering both intention-to-treat and per-protocol analysis and time and duration of exposure and time to event in analysis, are being taken into account to address these shortcomings.

In conclusion, the TLGS, as the oldest population-based cohort study in Iran besides the other Iranian large cohort studies, with precise detection of different outcomes has provided valuable evidence for prediction and prevention of NCDs in Iran and with some novelties in the world especially in the middle-income countries.

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Table 2. A Summary of the Incidence Rates of the Outcomes: Tehran Lipid and Glucose Study

	Event/Study Population	Mean Age (SD), y	Median Follow-up, y	Incidence Rate (95% CI), Per 1000 Person-Year	Ref.
Men					
CVD	458/2280	55.5 (10.73)	11.9	19.2 (17.5 - 21.0)	(9)
Premature CVD[a]	117/2235	40.0 (6.74)	11.74	5.68 (4.74 - 6.81)	(10)
CHD	320/2889	47.5 (12.3)	10.3	11.9 (10.6 - 13.2)	(11)
Stroke	90/1311	61.1 (7.8)	13.9	5.9 (4.8 - 7.2)	(12)
DM[b]	303/3620	42.2 (14.6)	9.5	10.2 (9.13 - 11.4)	(13)
Pre-DM[c]	853/2408	40.6 (13.9)	9.14	46.1 (43.0 - 49.2)	(14)
HTN[d]		40.7 (13.2)	6	30.9 (27.8 - 34.3)	(15)
Pre-HTN[e]	705/1466	38.1 (12.11)	9.2	76.4 (70.9 - 82.2)	(16)
ISH[f]	113/1908	40.1 (13.2)	9.57	6.6 (5.5 - 7.9)	(17)
IDH[g]	262/2057	38.8 (12.2)	9.57	14.5 (12.8 - 16.3)	(17)
MetS[h]	565/1161	40.6 (14.9)	9.3	74.9 (69.0 - 81.35)	(18)
CKD[i]	206/1454	41.3 (13.4)	9.9	13.26 (11.6 - 15.2)	(19)
Hypothyroidism[j]	61/2258	40.0 (14.0)	6.0		(20)
Hyperthyroidism[k]	15/2258	40.0 (14.0)	6.0		(20)
Thyroid autoimmunity[l]	77/2171	40.0 (14.0)	9.0	4.2 (3.4–5.3)	(28)
CVD-mortality	131/2280	55.5 (10.73)	11.9	5.5 (4.6 - 6.5)	(9)
All-cause mortality	341/2532	55.5 (10.73)	11.9	13.0 (11.7 - 14.5)	(9)
Women					
CVD	331/2774	53.2 (9.36)	11.9	11.0 (9.9 - 12.3)	(9)
Premature CVD[a]	176/3703	43.9 (9.42)	11.74	4.71 (4.07 - 5.47)	(10)
CHD	236/3803	46.3 (11.4)	10.3	6.5 (5.7 - 7.3)	(11)
Stroke	64/1436	58.8 (6.8)	13.9	3.6 (2.9 - 4.7)	(12)
DM[b]	433/4780	39.3 (13.1)	9.5	11.0 (9.99 - 12.0)	(13)
Pre-DM[c]	902/3051	37.9 (12.1)	9.25	36.8 (32.6 - 39.1)	(14)
HTN[d]		37.6 (11.4)	6	29.3 (26.7 - 32.1)	(15)
Pre-HTN[e]	735/2131	34.6 (10.05)	9.2	48.9 (45.5 - 52.6)	(16)
ISH[f]	122/2666	37.1 (11.2)	9.57	5.06 (4.2 - 6.04)	(17)
IDH[g]	208/2752	36.5 (10.6)	9.57	8.4 (7.3 - 9.6)	(17)
MetS[h]	552/1697	36.1 (12.1)	9.3	43.35 (39.9 - 47.12)	(18)
CKD[i]	517/1859	38.3 (12.0)	9.9	28.5 (26.2 - 31.1)	(19)
Hypothyroidism[j]	183/2803	40.0 (14.0)	6.0		(20)
Hyperthyroidism[k]	25/2803	40.0 (14.0)	6.0		(20)
Thyroid autoimmunity[l]	223/2849	40.0 (14.0)	9.0	9.3 (8.2 - 10.7)	(28)
CVD-mortality	69/2280	53.2 (9.36)	11.9	2.3 (1.8 - 2.9)	(9)
All-cause mortality	208/2986	55.5 (10.73)	11.9	6.5 (5.6 - 7.4)	(9)

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, type 2 diabetes; HTN, hypertension; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; MetS, metabolic syndroms.

[a] Premature CVD was defined as having a CVD event before the age of 55 and 65 years in men and women, respectively.

[b] DM defined as fasting plasma glucose $\geq$ 126 mg/dL or 2-h postchallenge plasma glucose $\geq$ 200 mg/dL or medication for diabetes.

[c] Pre-DM defined as fasting plasma glucose $\geq$ 100 mg/dL or 2-h postchallenge plasma glucose $\geq$ 140 mg/dL without overt diabetes.

[d] HTN defined as systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg or antihypertensive medication.

[e] Pre-HTN defined as systolic blood pressure $\geq$ 120 mmHg or diastolic blood pressure $\geq$ 80 mmHg without overt hypertension.

[f] ISH defined as systolic blood pressure $\geq$ 140 mmHg and diastolic blood pressure < 90 mmHg.

[g] IDH defined as systolic blood pressure < 140 mmHg and diastolic blood pressure $\geq$ 90 mmHg.

[h] MetS was defined using the joint interim statement and national cutoff for waist circumference.

[i] CKD was considered an eGFR below than 60 mL/min/1.73 m^2.

[j] Including both overt and subclinical hypothyroidisim. Total incidence rate (in men and women together) was 9.62 per 1000 person-year.

[k] Including both overt and subclinical hyperthyroidisim. Total incidence rate (in men and women together) was 1.6 per 1000 person-year.

[l] TPOAb-positive defined as TPOAb levels > 40 IU/mL.

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Tehran Thyroid Study (TTS)

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Abstract

Context: This review summarizes key findings of the Tehran thyroid study (TTS), a large scale community-based study with approximately a two decade follow-up, about the incidence, prevalence, and natural course of thyroid disorders as well as associations between thyroid diseases and metabolic syndrome (MetS), dysglycemia, and cardiovascular disease (CVD).

Evidence Acquisition: PubMed, Scopus, and Web of Science databases, and the library of Research Institute for Endocrine Sciences were used to search for TTS articles. Articles were subdivided based on the fields of prevalence, incidence and natural course, and associations of thyroid function with the incident hypertension (HTN), MetS and CVDs.

Results: The 2.5th and 97.5th percentiles of serum thyrotropin (TSH) were 0.32 and 5.06 mU/L, respectively. Estimated reference intervals (2.5th and 97.5th percentiles) for thyroid peroxidase antibody (TPOAb) levels were 1.5 - 32.8 and 2.1 - 35 IU/mL in men and women, respectively. Euthyroid persistency was 93.24% during 6 years. There was a negative association between free thyroxine (FT4) levels and insulin resistance. Decreasing FT4 values over time would predict MetS in euthyroid and subclinical hypothyroid subjects (TSH < 10 mU/L). The incidence of thyroid disorders in patients with diabetes, pre-diabetes and healthy controls was 14, 18, and 21 per 1000 person-years, respectively, indicating significantly lower incidence in individuals with diabetes compared to healthy controls. Serum FT4 within the reference range was positively associated with all blood pressure (BP) measures in the total population and in men; however, serum TSH was positively associated with only systolic BP (SBP), diastolic BP (DBP) and mean arterial pressure of men. No associations were found between various states of thyroid function and prevalence and incidence of CVD.

Conclusions: A well designed cohort study aimed to investigate the gap in knowledge regarding thyroid disorders can generate many hypotheses to be examined in randomized controlled trials.

Keywords: Tehran Thyroid Study, Metabolic Syndrome, Cardiovascular Disease

1. Context

Thyroid diseases have a high prevalence, ranking as the most common endocrine disorder after diabetes. The incidence and long term consequences of thyroid diseases have been evaluated in the Wickham's 20 year-survey, revealing the annual incidence of hypothyroidism to be 4.1 (3.3 - 5.0)/1000 survivors/year and 0.6 (0.3 - 1.2)/1000 survivors/year in men and women, respectively. The mean incidence of hyperthyroidism in women was 0.8 (0.5 - 1.4) /1000 survivors/year (1). Subclinical hypo- and hyperthyroidism affect 5 - 15% and 1 - 2.1% of the general population, respectively (2).

The Tehran thyroid study (TTS), a prospective population-based cohort study, is being conducted within the framework of the Tehran lipid and glucose study (TLGS) (3). Of the TLGS participants, 5786 were randomly selected between March 1997 - December 2004 to participate in the TTS to investigate of the epidemiology of thyroid diseases and their long term consequences with regards to the metabolic diseases, CVD and mortality in the iodine sufficient population of Tehran (4). This review briefly presents the key findings from studies conducted on this cohort and summarizes several contemporary TTS publications on different aspects of thyroid diseases.

2. Evidence Acquisition

PubMed, Scopus, and Web of Science databases, and the library of Research Institute for Endocrine Sciences were used to search for TTS articles. Articles were subdivided based on the fields of prevalence, incidence and natural course, and associations of thyroid function with the incident hypertension (HTN), MetS and CVDs.

3. Results

3.1. Reference Values of Thyroid Function Tests in the Iranian Population

The appropriate population specific, gender and age-related reference intervals for thyroid-stimulating hormone (TSH) and free thyroxine (FT4) are necessary to interpret results of thyroid function tests and determine the epidemiological prevalence of thyroid dysfunction in any population. We determined thyroid hormones normal ranges in our population, an iodine sufficient population. According to the National Academy of Clinical Biochemistry (NACB) criteria, the mean ± SD and median (interquartile range [IQR]) for TSH were 1.77 mU/L ± 1.24 and 1.46 (0.93 - 2.23) mU/L, respectively. The 2.5th and 97.5th percentiles of TSH were 0.32 mU/L and 5.06 mU/L respectively. The mean ± SD and median (IQR) for FT4 for all negative thyroid peroxidase antibody (TPOAb) subjects were 1.19 ± 0.16 and 1.18 (1.08 - 1.31) ng/dL, respectively (4). Regarding reference intervals for TPOAb, 2.5th and 97.5th percentiles were 1.5 - 32.8 and 2.1 - 35 IU/mL in men and women, respectively. No significant difference in age categories was observed. To predict clinical and subclinical hypothyroidism, optimal cutoff points for TPOAb were 18.38 and 14.77 IU/mL, respectively (5). The geometric mean and overall upper reference limit of TSH were 1.40 and 4.12 mIU/L in the National health and nutrition examination survey (NHANES III) from the United States of America (6); corresponding values for TSH in the Chinese population were 1.90 and 0.59 - 5.98 mIU/L, respectively (7).

Overall different iodine intakes, hereditary and genetic influences on the set-point of thyroid hormones such as polymorphisms in thyroid hormone pathway genes and FT4/TT4, TSH assay methods might be reasons for the variety in upper limits of TSH in different populations (8). Determination of population specific reference limits for thyroid tests helps to classify and manage thyroid diseases accordingly.

3.2. Prevalence and Incidence of Thyroid Disorders

Epidemiology of thyroid disorders depends on various ethnic and geographical factors (9). Table 1 shows prevalence and incidence of thyroid dysfunction states reported in the TTS. Over a 6-year follow-up, the annual incidence rates of subclinical and overt hypothyroidism were 7.62 (95% CI 7.39 - 7.85) and 2.0 (95% CI 1.94 - 2.06] per 1000 persons, respectively. Annual incidence rates of subclinical and overt hyperthyroidism were 0.92 (95% CI 0.90 - 0.95) and 0.68 (95% CI 0.66 - 0.70) per 1000 persons, respectively (10).

In the Amouzegar et al. study (11) within the framework of the TTS, overall, 12.8% were TPOAb positive, with higher prevalence among women than in men (16.0 vs. 8.5%, P = 0.001). The prevalence of TPOAb positivity in the total population was 11.9, 14.9 and 13.6% in the young, middle aged and elderly, respectively. The total incidence rate (95% CI) of TPOAb positivity in the total population was 7.1 (6.36 - 7.98) per 1000 person-years of follow-up; this rate was higher among young participants [8.5 (7.5 - 9.7) per 1000 person-years. Sex stratified analysis showed that TPOAb positivity was higher in women, being 9.3 (8.2 - 10.7) per 1000 person-years. Based on the Cox proportional hazard model, the hazard of developing TPOAb positivity was higher in women, and those with younger age and higher serum TSH concentrations. Moreover, development of TPOAb positivity in each phase was significantly associated with increasing TSH concentration during the seroconversion phase, compared to baseline levels (11).

Prevalence of hypothyroidism was 0.5% in men and 7.1% in women in the Vanderpump et al. (1) study (12) and these values were 0.9% and 4.8% in the HUNT study, respectively (13). Flynn et al. reported 3,486 incident cases of primary hypothyroidism with incidence rate (95% CI) of 4.98 (4.81 - 5.17)/1000 person-years in women and 0.88 (0.80 - 0.96)/1000 person-years in men.

3.3. Natural Course of Thyroid Function

Euthyroid persistency was 93.24% during 6 years. Predictive factors for conversion to thyroid dysfunction were TSH, FT4 and TPOAb levels, sex, and smoking. Criteria for early diagnosis of hypothyroidism (i.e., 94% sensitivity and 82% specificity, P < 0.0001) were obtained based on baseline and 3-year follow-ups of thyroid function tests and TPOAb. Early diagnosis of hypothyroidism was significantly associated with impaired glucose tolerance (relative risk [RR] 3.03 [CI 1.36 - 6.75]), high cholesterol (RR 2.46 [CI 1.45 - 4.18]), obesity (RR 2.92 [CI 1.64 - 5.2]), and hypertension (RR 1.68 [CI 1.53 - 1.84]) (10).

The Effraimidis et al. study showed that baseline higher TSH, lower FT4 serum levels and presence of TPOAb are among risk factors for progression of euthyroidism to hypothyroidism (14).

3.4. Thyroid Function and Body Mass Index

Considering the intriguing relationship between the thyroid and weight status, the association between body mass index (BMI), as the outcome, and changes of thyroid function tests within the reference range, as the predictor,

Table 1. Epidemiology of Thyroid Dysfunction States in the Tehran Thyroid Study (TTS)[a,b]

	Prevalence, %	Incidence [Per 1000 Person-Years (95% CI)]
Subclinical hypothyroidism	5.5	7.62 (7.39 - 7.85)
Overt hypothyroidism	2.0	2.0 (1.94 - 2.06)
Subclinical hyperthyroidism	3.7	0.92 (0.90 - 0.95)
Overt hyperthyroidism	2.2	0.68 (0.66 - 0.70)

[a] Adopted from reference (10).
[b] Definitions: Subclinical hypothyroidism: serum TSH > 5.06 mU/L with normal FT4 level. Overt hypothyroidism: serum TSH > 5.06 mU/L and FT4 < 0.91 ng/dL. Subclinical hyperthyroidism: serum TSH < 0.34 mU/L and normal FT4 level. Overt hyperthyroidism: serum TSH < 0.34 mU/L with serum FT4 > 1.55 ng/dL.

in 1100 normal-weight participants at baseline was investigated over a 10-year follow-up (15). Modified Poisson regression analysis for binary outcome (BMI < 25 or ≥ 25 kg/m^2), after adjustment for age, sex, smoking, and TPOAb status, showed a negative association between ΔFT4 and follow-up BMI (relative risk, 95% CI: 0.55 [0.37 - 0.80]) without any significant association between ΔTSH and follow-up BMI (relative risk, 95% CI: 0.99 [0.96 - 1.01]). Moreover, in multinomial logistic regression analysis, no associations were observed between changes of serum FT4 or TSH and different categories of follow-up BMI (normal BMI, overweight, and obese) for either overweight or obese vs. normal-weight participants.

3.5. Thyroid Function and Metabolic Syndrome

Thyroid hormones have pleiotropic effects on different components of metabolic syndrome (MetS) and abnormal thyroid function may have a role in the development of MetS (16).

3.5.1. Metabolic Syndrome in Clinical and Subclinical Hypo- and Hyperthyroid States

Associations of thyroid dysfunction with MetS are not clearly defined. Results of a study from the TTS (17) showed that overt and subclinical hypothyroidism are associated with MetS and two of its components, i.e. abdominal obesity and hypertriglyceridemia, especially in the elderly and hyperthyroidism may be associated with impaired fasting glucose. Moreover, overt hypothyroidism was predictor of MetS only in male population; a gender difference possibly due to the fact that most women in this study were premenopausal, therefore, the advantageous effects of estrogen may inhibit progression to MetS. On the other hand, BMI in women was significantly higher than in men; higher TSH values could be related to obesity rather than a true hypothyroidism. After age stratification, the risk of MetS was significantly higher only in subclinical hypothyroid subjects, aged > 50 years even after adjustment for sex, BMI and smoking.

3.5.2. Metabolic Syndrome in the Euthyroid State

There is conflicting data on associations of thyroid function tests within the reference range with MetS. Investigation of this subject in the TTS (18) indicated that lower normal FT4 concentrations were significantly associated with higher risk of insulin resistance and MetS; findings did not change after excluding individuals with positive TPOAb (18).

3.5.3. Metabolic Syndrome and Long Term Thyroid Hormone Variations

There is controversial data regarding the association of the TSH and FT4 with MetS and its components, mostly from studies with a cross-sectional design, which hampers determining a cause and effect relationship. Associations of thyroid hormone variations in subclinical and euthyroid ranges with the incidence of MetS and its components were assessed over a 10 year follow-up (19) and showed decreasing FT4 values (not TSH) over time would predict MetS in euthyroid and subclinical hypothyroid subjects (TSH < 10 mU/L). Each ng/ml decrease in FT4 was associated with 40% increased risk of MetS within 10 years, after adjustment for sex, age, and smoking, an association that disappeared after BMI adjustment. FT4 values could predict the incidence of MetS especially in non-obese adults with normal or subclinical thyroid function. Cumulative effect of FT4 decline over 10 years, at 4 follow-ups, was predictive for abdominal obesity and higher triglyceride values after adjustment for age, sex, BMI and homeostasis model assessment-insulin resistance (HOMA-IR); therefore, it seems that other mechanisms, except for BMI and IR may be responsible for the association of these metabolic abnormalities and FT4. Moreover, this study showed a negative association of FT4 with IR (19).

TSH was not associated with incidence of MetS or any of its components in the crude or adjusted models, except for serum triglycerides (TGs) and waist circumference; the relationship between TSH and TGs remained even after fur-

ther adjustment for HOMA-IR and BMI indicating that the relationship of TSH and TGs may be modified by mechanisms other than IR and BMI.

3.6. Thyroid and Insulin Resistance

In a cross-sectional study, associations of thyroid hormones within the reference range and TPOAb with IR were investigated in 2758 euthyroid subjects (20). Multivariate linear regression analysis revealed a positive association between serum TSH and HOMA-IR (β = 0.05, P = 0.01) and a negative association of FT4 and HOMA-IR (β = -0.06, P < 0.01) only in men. The multiple logistic regression analysis based on the presence or absence of IR showed that higher serum FT4 was associated with lower risk of IR in men [odds ratio (OR): 0.27, 95% CI 0.12 - 0.61]. No relationship was reported in women. Moreover, there were no significant differences in HOMA-IR, fasting insulin or fasting blood glucose between the TPOAb-negative and -positive groups (20).

3.7. Thyroid Dysfunction in Patients with Impaired Glucose Metabolism

In the TTS, for the first time, the prevalence, incidence and predictive factors of thyroid disorders in individuals with dysglycemia were assessed; the incidence of thyroid diseases among 435 individuals with diabetes, 286 individuals with pre-diabetes, and 989 healthy controls at baseline was 14, 18, and 21 per 1000 person-years, respectively, being significantly lower in those with diabetes than in healthy controls; this difference was not significant after adjusting for covariates. Participants with baseline serum TSH > 1.94 mU/L or TPOAb $\geq$ 40 IU/mL had higher risk for incidence of thyroid diseases compared to those with TSH $\leq$ 1.94 mU/L or TPOAb < 40 IU/mL in all mentioned three groups. Baseline TSH > 1.94 mU/L was predictive of thyroid diseases with 70% sensitivity and specificity. We showed that baseline serum TSH (receiver operating characteristic [ROC] area, 95% CI: 0.73, 0.68 - 0.77) had better predictive value than TPOAb (ROC area, 95% CI: 0.65, 0.61 - 0.69) for development of thyroid diseases. Incidence of thyroid diseases in patients with type 2 diabetes or pre-diabetes was not higher than in healthy controls (21).

3.8. Thyroid Function and Blood Pressure

To investigate the association of different blood pressure (BP) components with serum TSH and FT4 levels in euthyroid subjects, 4,756 euthyroid individuals with mean (SD) age of 40.1 $\pm$ 14.38 years were selected (22). Three tertiles of serum TSH were defined as follows: 1st (0.32 < TSH < 1.21 mU/L), 2nd (1.21 - 2.07 mU/L) and 3rd (2.07 - 5.06 mU/L) tertiles. Negative associations between TSH and systolic BP (SBP) in the first and second TSH tertiles and between TSH and pulse pressure (PP) in the second TSH tertile were reported. No significant association was detected between TSH and diastolic BP (DBP) or mean arterial pressure (MAP) in different TSH tertiles. Serum FT4 levels of individuals in the first TSH tertile were significantly associated with MAP. There were also significant relationships between serum FT4 and DBP in the first and second TSH tertiles. After adjustment for BMI, smoking status, gender and age, the association between TSH and SBP, DBP, PP and MAP did not reach a significant level in any of TSH tertiles; increased FT4 concentrations were associated with elevated DBP in the third tertile, and SBP, MAP and PP in all tertiles. In the logistic regression analysis, different TSH tertiles were not associated with HTN (22).

Moreover, to investigate the associations of serum TSH and FT4 within the reference range with different BP measured also incident prehyperetension (preHTN) and HTN, a longitudinal survey on 2282 individuals was performed during a 9-year follow-up. Multivariate-adjusted generalized estimating equation (GEE) analysis revealed a decreasing trend for all BP parameters throughout the study period, either adjusted for serum TSH or FT4 levels. Serum FT4 within the reference range was positively associated with all BP measures in total population and in men; however, serum TSH was positively associated with only SBP, DBP and MAP of men. No associations between serum TSH within the reference range and BP status were detected in multivariate transitional model; however, a 1 ng/dL higher FT4 was associated with 40% increased risk of preHTN [OR (95 % CI), 1.40 (1.02 - 1.90)], but not with HTN [OR (95 % CI), 0.93 (0.80 - 1.09)] (23).

3.9. Thyroid Function and Obesity Phenotypes

The relationship between thyroid function and different obesity phenotypes during 9 years was examined in 1938 euthyroid individuals from the TTS (24). Multivariate GEE analysis showed that each 1 ng/dL increment in FT4 levels within the reference range was accompanied with a 1.65-fold (95% CI: 1.09 - 2.5) increase of developing the metabolically healthy normal weight phenotype. Moreover, each 1.0 ng/dL increment in FT4 within the reference range was associated with a 50% decreased risk of developing the metabolically healthy obese phenotype [OR (95% CI): 0.50 (0.32 - 0.76)]. Regarding serum TSH, a significant positive association was found between serum TSH and development of the metabolically unhealthy normal weight

phenotype [OR (95% CI): 1.22 (1.01 - 1.48)].

3.10. Thyroid Dysfunction and Incident Cardiovascular Events

To investigate the relationship between different thyroid function states and the incidence of (CVD)/coronary heart disease (CHD) in the TTS, 3975 participants were selected. During a median follow-up of 11.2 years, 400 CVD events occurred. No association was observed between different thyroid dysfunction states and incidence of CVD/CHD even after the age and sex adjustment. The multivariable hazard ratios (95% CI) of subclinical hypothyroidism, hypothyroidism, subclinical hyperthyroidism, and hyperthyroidism for CVD events were 1.21 (0.77 - 1.88), 0.76 (0.33 - 1.69), 0.81 (0.46 - 1.41) and 1.48 (0.70 - 3.16), respectively (25). These findings indicate that different thyroid dysfunction states have no associations with CVD or CHD during 11 years of follow-up in a cohort with high prevalence and incidence of CVD.

4. Conclusions

This paper has summarized many of the key findings related to thyroid disorders including sex and age specific population based reference ranges of thyroid function tests, prevalence, incidence, risk factors, risk prediction for thyroid diseases and the natural course of thyroid function. Routine screening for thyroid function in healthy individuals residing in areas of iodine sufficiency is controversial. The need for such screening should fulfill all criteria for mass screening (26), indicating that its benefit outweighs the physical and psychological harm caused by efforts involved in screening. Investigators of TTS are currently in the process of collecting and analyzing data after 18 years of follow-up of thyroid function tests and serum TPOAb in this population and the results obtained may add more clues for mass screening for thyroid function. This is because although the prevalence of overt dysfunction is low, but a substantial proportion of adults have subclinical hypo- and hyperthyroidism. It is hoped that a prospective population based study such as TTS, would shed more light on the occurrence of outcomes such as death, CVD, glucose intolerance, insulin resistance, MetS, quality of life, etc. It is noteworthy to know that all of these outcomes are available in the data of TLGS, the mother project of TTS. This information may also disclose any potential evidence-based therapy for subclinical thyroid disorders. Results of the TTS add to global data knowledge and could be especially applicable to Caucasian populations. Further fundamental studies are needed to confirm the cause and effect relations in the field of thyroid hypo- and hyper function and cardiovascular outcomes and in cancer development.

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Reproductive Assessment: Findings from 20 Years of the Tehran Lipid and Glucose Study

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Abstract

Context: Reproductive domains of the Tehran lipid and glucose study (TLGS) are unique in that they provide reliable information on reproduction of an urban population of West Asia. The aim of this review is to present the most important reproductive findings of TLGS.

Evidence Acquisition: This review is summarizing all articles published in the context of reproductive aspects of TLGS results over the 20-year follow-up. A comprehensive databases search was conducted in PubMed (including Medline), Web of Science and Scopus for retrieving articles on the reproductive histories in context of the TLGS.

Results: The mean (SD) age at menarche and menopause was 13 (1.2) and 49.6 (4.5) years respectively. While pills were the most commonly used modern methods at the initiation of TLGS, the prevalence of condoms rose sharply and significantly over the follow up duration. Among women with history of gestational diabetes, the risk of diabetes and dyslipidemia progression were 2.44 and 1.2 fold higher than others. Prevalences of PCOS and idiopathic hirsutism among reproductive age participants of TLGS were 8.5% (95% CI: 6.8% - 10.2%) and 13.0% (95% CI: 10.9% - 15.1%), respectively. Trend of cardio-metabolic risk factors among women with PCOS showed that there were no statistically significant differences between mean changes of each cardio metabolic variables between PCOS and healthy women; PCOS status also significantly associated with increased hazard of diabetes and prediabetes among women aged younger than 40 years (HR: 4.9; 95% CI: 2.5 - 9.3, P value < 0.001)) and (HR: 1.7; 95% CI: 1.1 - 2.6), P value < 0.005), respectively.

Conclusions: The population based nature of TLGS provides a unique opportunity for valid assessment of reproductive issues, the results of which could provide new information for modification of existing guidelines.

Keywords: Reproductive Histories, Tehran Lipid and Glucose Study

1. Context

There are a limited number of cohort studies that provided the population based evidences on reproductive histories of both male and females in reproductive life span and research in this area has been clearly insufficient. Reproductive disturbances and their consequences are mainly defined according to data derived from clinical settings or case control studies that suffer from many shortcomings. For instance, the current definition for polycystic ovary syndrome (PCOS) seems to be premature and may have unwanted negative influence on research, clinical practice, and quality of life. As a result societies on reproductive endocrinology endorse the immediate and considerable need for future research into PCOS, its phenotypes and morbidities in population settings (1).

Data collected on reproductive domains in Tehran lipid and glucose study (TLGS) is one of the unique data that provide reliable information on reproduction of an urban population of West Asia. Using valid tools for assessment of various aspects of reproductive history including structured questionnaire, comprehensive physical exam, thoughtful checking of previous medical history and hospital records and universal biochemical and hormonal assessment, provide a valuable data set for investigating some gaps in knowledge in the context of a population-based cohort. Menarcheal and menopausal age and their influencing factors, contraceptive behaviors

of participants and its trend, infertility, pregnancy complications and androgen excess disorders are some topics that been reported in this paper.

2. Evidence Acquisition

This review was summarizes all articles published in the context of reproductive aspects of TLGS over the 20-year follow-up. For this purpose, a comprehensive dataset search was conducted in PubMed [including Medline], Web of Science and Scopus for retrieving papers on the reproductive histories in context of the TLGS. The following MeSH keywords were used for the search: "menarche" OR "menopause" OR "contraception" OR "diabetes, dyslipidemia, hypertension progression after pregnancy" OR "infertility" OR "androgen excess disorders" OR "polycystic ovary syndrome" OR "hirsutism" OR "menstrual cycle irregularity" OR "cardio-metabolic disturbance" AND "Tehran lipid and glucose study".

In TLGS a comprehensive questionnaires on reproductive lifespan including menarche, menopause, menstrual regularity, parity, abortion, type and duration of contraception usage, infertility, and lactation were collected through face to face interviews by trained staff. Pregnancy complications were assessed based on self-reports using the standard definition for each complications. Androgen excess manifestation were evaluated using valid tools. The hirsutism scores were evaluated using the modified Ferriman-Gallwey (mFG) scoring scale. Acne was assessed based on its type, number and distribution. Blood samples of participants were collected at each visit. Serum concentrations of biochemical parameters were measured immediately and rest of the sera was stored at -80°C for future assessments. For purpose of hormonal assessments, fasting venous blood sampling were collected on the third day of spontaneous or progesterone withdrawal menstrual period. Transvaginal ultrasound scans of the ovaries was performed for non-virgin participants by an experienced specialist in the same day as the blood samples were obtained.

3. Results

3.1. Menarcheal Age; Trend and Its Influencing Factors

The first menstruation or menarche, the latest event in female's puberty, is a landmark in the reproductive life span of a woman, which is influenced by various genetic and environmental factors, including race, socioeconomic status of family, geographic region, nutritional status, physical activity and body mass index (BMI), psychological factors and smoking (2, 3). The TLGS study has 6 follow-up phases at approximately 3 year intervals. Age at menarche was assessed in the second phase of study, using face to face interview, assessments that were repeated in each phase of TLGS; mean (SD) age at menarche in TLGS participants was 13 (1.2) years (3); there was a negative secular trend resulting a reduction in age at menarche from 13.8 years to 12.9 years in women born between 1930 - 1990. This negative secular trend was associated with a positive trend in mean of height. In this respect, while the mean age at menarche reduced by 0.15 years per decade; mean height elevated by 0.99 cm per decade (4). Contradictory data have been documented on the secular trend of age at menarche in different societies; while studies from Denmark and the Netherlands show no any decrease in age at menarche since 1960 (5, 6), studies from Brazil, the USA, South China, Mexico and Korea reported a significant negative trend in the age of puberty and menarche (7-9).

Among the influencing factors, data collected in TLGS revealed that maternal education, and maternal age at menarche, pre-menarcheal BMI, pre-menarcheal nutrition affect menarcheal age; the risk of earlier menarche was increased in participants with higher milk consumption [OR: 2.28; 95% CI: 1.03 - 5.05], Calcium [OR:3.20; 95% CI: 1.39 - 7.42], magnesium [OR: 2.43; 95% CI: 1.12 - 5.27] and phosphor [OR: 3.37; 95 % CI: 1.44 - 7.87) after adjusting for energy and protein consumption and maternal age at menarche (10). There was no significant correlation between age at menarche and mother's job, physical activity, lipid profiles and calorie intake during pre-menarcheal years (2). Among all of these factors, premenarcheal BMI is modifiable and may prevent early or late menarche (3).

Timing of menarche has several potential health implications during women's life. In this respect, early menarche is associated with breast cancer (11), T2 diabetes mellitus (MD) (12), metabolic syndrome (MetS), cardiovascular events (CVD) and all-cause mortality (13). The results of TLGS showed that early menarche (< 11 years) was related to increased risk of DM and pre-DM, compared to the control group (13 - 14 years); (OR = 3.55; 95% CI: 1.6 - 7.8 and OR = 2.55; 95% CI: 1.4 - 4.8), respectively. This added risk remained unchanged after adjustment for other potential confounders including family history of DM, parity, educational level, anthropometric characteristics of age, BMI and waist circumference (WC), smoking status, physical activity, and duration of hormonal use (14).

3.2. Menopause and Its Cardio-Metabolic Consequences and Prediction of Menopausal Age

Menopause is an important milestone in the reproductive life of women. There is remarkable variation in the age at menopause. Age at menopause is naturally influenced by a variety of racial, environmental, genetic, behavioral and physiological factors. In TLGS, menopause was defined as the time of cessation of menstrual cycle for 12 consecutive-months, not due to vasectomy or any other biological or physiological factors; this information was collected from the first phase of study through direct interviews, and again in each further phase of TLGS.

Mean age at menopause of TLGS participants was 49.6 (4.5) years (15). There was a significant correlation between age at menopause, age at menarche, smoking history, and parity; it was lower among ever smoker, but increased with increasing age of menarche, and parity. However, we did not found any association between age at menopause and other demographic, anthropometric or reproductive characteristics of participants during reproductive period. In agreement with our findings, Mohammad et al. were reported the similar menopausal age in a national survey (mean 50.4, median 49.6 years). There was a positive secular trend (16); means for menopausal age of women born in the 1930s, 1940s, and 1950s were 48.5, 49.5 and 49.9 years respectively, a trend that remained even after adjusting for possible confounding factors. Worldwide data on secular trends of menopausal age are inconsistent, although they increased by approximately one year in Finland, Sweden and the USA in women born after the 1930s (17, 18), these findings differ to those of other studies conducted on 3944 white women (19) and a systematic review of observational studies (20).

Menopausal age is directly associated with the number of remaining both ovarian, indicating that serum concentration of anti mullerian hormone (AMH) can be considered a predictor for estimating age at menopause. The ongoing status of TLGS and the availability of frozen base line serum enables us to use statistical modeling for prediction of age of menopause using AMH serum concentration (21-23). Accurate estimation of menopausal age could identify those at higher risk of CVD, osteoporosis, and all cancers related to early or late menopause. Moreover, the estimation of the age at menopause is an extremely important information for women who plan to delay their childbearing. Identification of women who reached menopause during the study follow ups gives us the opportunity to check the reliability of our models. In the Bland and Altman method, the median difference between actual and predicted age at menopause was 0.51 years (SD = 2.45, range, -3 5.4 to 9.2 years) showing good agreement between the two. Additionally the graphical representation of menopause-free survival, using the Kaplan Meier plot showed similarity of survival experiences when actual and predicted ages at menopause were compared (Figure 1).Furthermore, collaboration with the Department of Reproductive Medicine of the University Medical Centre Utrecht, UMCU, Netherlands enabled us to assess the external validity of our model.

Reproductive aged women with various follicular reserve statuses may have different risk for cardiovascular events; to assess this assumption, we calculated age-specific anti-Müllerian hormone for individual reproductive age participant of the TLGS to consider the silent coronary artery disease (CAD) among women with various ovarian reserve statuses. We founded that anti-Müllerian hormone was not a marker for silent CAD.

Menopause was associated with increasing the risk of cardio-metabolic disturbances including decreasing high density lipoprotein cholesterol (HDL-C) and increasing diastolic blood pressure (DBP), low density lipoprotein cholesterol (LDL-C), triglycerides (TG), total cholesterol (24), fasting plasma glucose (FPG) and waist circumference (WC). The prevalence of metabolic syndrome during menopausal transition in TLGS was 53%, 54%, and 69% in pre-menopause, menopause, and postmenopause respectively (25, 26). The risk of diabetes and hypertension was increased in postmenopausal women (27). Despite elevated serum levels of TC and LDL-C after menopause in TLGS (26), there was no increase in numbers of cardiovascular events, possibly due to the lack of adequate years of follow up of cohort members.

The cardio-metabolic consequences of surgical menopause was compared with natural menopause in the TLGS and results revealed that metabolic disturbances were more common among menopausal women undergoing vasectomy compared to natural menopause (46.2 vs. 20.5 % respectively, P value < 0.01) (28).

In TLGS we found that menopausal status per se is related to elevated serum concentration of nitric oxide. Nitric oxide plays an important role in the protection from cardiovascular disease and its progression (29, 30).

3.3. Trend of Contraception Behavior

Contraception methods of couples have an important influence on the women health; improving the autonomy of women in modern societies, substantially influencing gender equality, increasing women's empowerment and reduces the poverty and mortality (31). During the previous

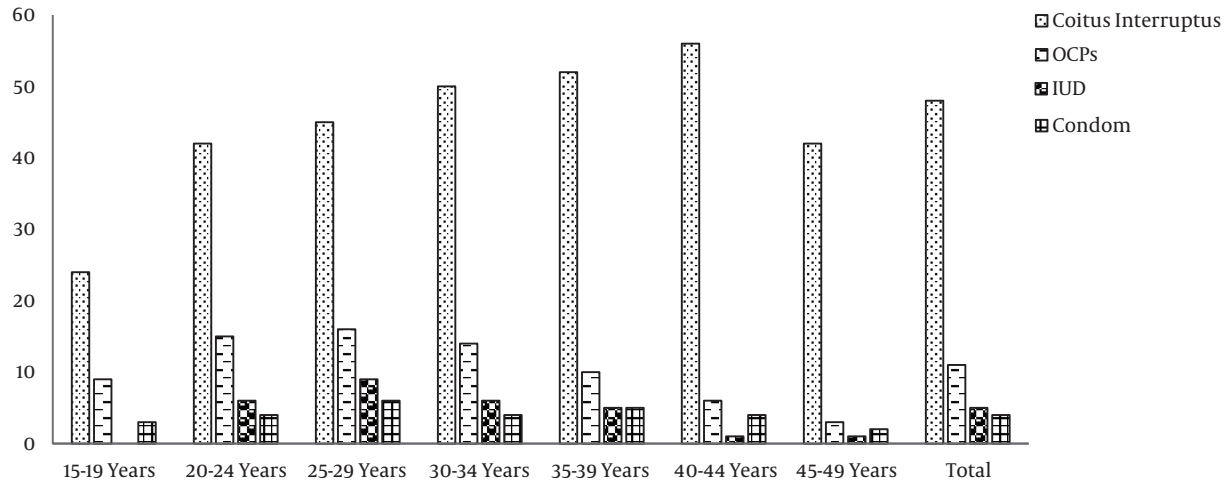

Figure 1. Percentages of family planning methods used by couples based on age groups in the first phase of the Tehran Lipid and Glucose

decades, Iranian population experienced the largest and fastest fertility decline around the world. Iran's traditionally pronatalist culture provides a favorable environment for high fertility. The 1986 national census showed a more than 3 percent annual population growth rate (32). The antinatalist policy and socio-political changes toward low fertility in Iran was officially initiated in 1988 (33). In this respect, Statistical Center of Iran in 1998 (same year as TLGS initiation) confirmed the signs of below-replacement fertility in Iran after the Population Growth Estimation Survey (PGES) in 1998 (same year as TLGS initiation). Despite Iran's successful family planning programs, Iran has overshot the target. The level of reduction in the total fertility rate to below birth replacement status has become a serious concern for politicians, encouraging the support of the pronatalist policy to increase population growth rates.

In the first phase of TLGS, the use of contraceptive methods during the last three months including OCPs, (LD contraceptive, HD contraceptive, Dian, Minipill and Triphasic pills), intrauterine devices (IUDs), Norplant, condoms, coitus interruptus and other methods were determined by a standard questionnaire of TLGS, during face-to-face interviews. The scientific committee of TLGS proposed the modification of reproduction data including contraception methods after phase 2 (3 years after initiation). In this respect, data on the contraceptive methods of vasectomy, tubal ligation, depo-provera injections and whether or not contraception usage were ontained and documented separately. The ongoing nature of TLGS enables us to assess trends of contraception use in Iran, especially after the recent population policies implementation.

According to the results of the first phase of TLGS, coitus interrupts, COCs, condom and IUD were used by 48, 11,4 and 5% of the individuals, respectively; 32% used no contraception, with no significant differences in contraceptive use behavior among various age groups (Figure 1) (34).

However the contraceptive behaviors of TLGS participants changed overtime; while pills were the most commonly used modern methods at initiation of the TLGS, condom was the most commonly used method in the last phase of study; the proportion of condom use sharply and significantly increased from 10.9% in 2002 to 21.9% in 2011 (Table 1) (35).

3.4. Oral Contraceptive Usage and Cardio-Metabolic Disturbance

Since contraceptive usage have been showed as a risk factor for vascular thromboembolism and cardiometabolic disorders, the impact of oral contraceptives on some cardio-metabolic parameters including hypertension, hypercholesterolemia, hypertriglyceridemia, obesity and metabolic syndrome was determined in TLGS.

According to duration of oral contraceptive usage in four sub-groups, i.e. non-users, less than 11 month users, 12 - 35 month users, and $\geq$ 36 month users; cardio-metabolic parameters did not have statistical significant between these sub-groups, after further adjustment for potential confounders of age, parity and education, except for hypercholesterolemia which was significantly 1.5 times higher

Table 1. Prevalence Percentages of Women by Contraceptive Use, Based on TLGS Phase

Year	N	Modern, n (%)							Traditional[a], n (%)	None, n (%)
		Pill	IUD	Female Sterilization	Male Sterilization	Condom	Injection	Total		
2002	2506	377 (15)	433 (17.2)	228 (9)	214 (8.5)	275 (10.9)	14 (0.5)	1541 (61.4)	645 (25.7)	320 (12.7)
2005	2529	323 (12.7)	385 (15.2)	214 (8.4)	226 (8.9)	385 (15.2)	10 (0.3)	1543 (61)	778 (30.7)	208 (8.2)
2008	2594	248 (9.5)	323 (12.4)	181 (6.9)	216 (8.3)	519 (20)	10 (0.3)	1497 (57.7)	849 (32.7)	248 (8)
2011	2525	153 (6)	198 (7.8)	172 (6.8)	203 (8)	553 (21.9)	10 (0.3)	1289 (51)	874 (34.6)	362 (14.3)

[a] Rhythmic, withdrawal or periodic abstinence.

among women who used OCPs for more than 36 months compared to others (OR 1.5; 95 % CI: 1.01 - 2.2) showing the cardio-metabolic safety of COPs consumption for less than 3 years in TLGS women (36).

3.5. Infertility

The prevalence and causes of primary infertility were assessed in TLGS population. Infertility was defined as inability to conceive after a 12 months of sexual intercourse, without using any contraception. Primary infertility was defined as the "incapacity to become pregnant within one year of exposure to pregnancy among women aged 15 - 49 years". The overall prevalence of primary infertility was 17.3%. According to the logistic regression analysis, primary infertility was independently associated with age (OR: 1.3; 95% CI: 1.1 - 13.6, P value = 0.001), BMI (OR: 1.9; 95% CI: 1.8 - 4.1, P value < 0.001), smoking status (OR: 1.4; 95% CI: 1.3 - 3.5, P value = 0.012) and higher educational level (OR: 2.2; 95% CI: 1.1 - 5.5, P value = 0.03). Our prevalence however is lower than those of low-to-middle-income countries (34.1%, 95% CI: 30.3 - 39.3%) (37), and is higher than those of western countries which is approximately 11.5% (95% CI: 10.2, 12.9) (38).

3.6. Incident Diabetes Type 2 and Dyslipidemia in Relation to Previous Gestational Diabetes Mellitus: Contributions of the Tehran Lipid and Glucose Study

Several studies have investigated cardio-metabolic disturbances following GDM. However, a 20-year follow-up evaluation of GDM outcomes is one of the unique contributions provided by TLGS in this field. In the present review, we highlight our findings on T2DM and dyslipidemia incidence and major influencing factors after a history of GDM.

3.6.1. Type 2 Diabetes After Gestational Diabetes

In TLGS, gestational diabetes (GDM) women were assessed based on a self-reporting questionnaire asking about their history of GDM. At initiation of TLGS, GDM was defined based on the World Health Criteria (39) and universal screening was part of routine prenatal care. In TLGS, the median (IQR) for follow-up years of GDM and non-GDM were 12.1 (8.09 - 13.51) and 11.62 (6.2 - 13.1), respectively. The odds of diabetes progression was more that two fold higher in women with prior GDM, compared without history of GDM. The adjusted odds was 2.1 (P value < 0.001, CI: 1.5 - 3).

Survivor function indicated significantly different results between GDM and non-GDM women, indicating shorter interval until T2DM progression in GDM-affected women compared with their healthy counterparts, (6.95 years [IQ: 4.22 - 10.71]) vs. (8.45 years [IQ: 5.08 - 10.89]), (P value < 0.001), respectively (Figure 2). The total cumulative incidence rate of diabetes at the median follow-up time was 9/1000 (CI = 5/1000 - 12/1000) and 4/1000 (CI = 1/1000 - 6/1000) in GDM and non-GDM women, respectively.

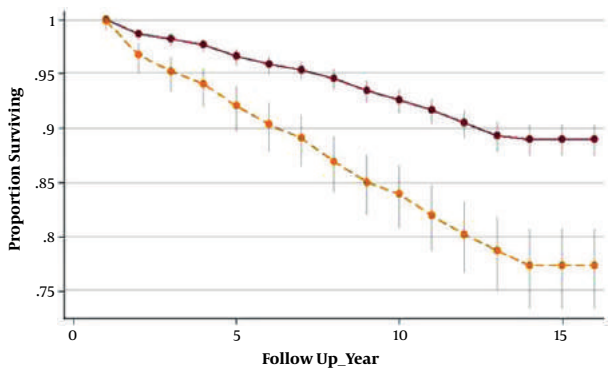

Figure 2. Survivor function (95% CI) using Kaplan-Meier analysis between GDM and non-GDM groups. Upper line: (non-GDM) non-gestational diabetes mellitus group; Lower line: (GDM) gestational diabetes mellitus group

We found that each one unit increment in BMI raised the odds of T2DM for a minimum of 0.08% and maximum of 15% (OR: 1.13, CI: 1.08 - 1.15). Moreover, of the several predisposing factors, family history of T2DM was associated with 1.7 fold higher risk of emerging diabetes in GDM group (OR: 1.76, CI: 1.24 - 2.5).

3.6.2. Dyslipidemia as a Consequence of Gestational Diabetes

Of a total of 4076 reproductive aged women, with at least one history of pregnancy, 2604 subjects were excluded due to baseline dyslipidemia, and missing or incomplete data. Of the remaining 1472 women, 289 had history of prior GDM and 1183 did not have history of GDM. Median (IQR) for follow-up years in women with and without prior GDM were 7.48 (2.1 - 12.4) and 8 (2.5 - 12.3), respectively. The odds ratio of dyslipidemia development was more than 1.2 fold higher in women with prior GDM. However after adjustment for age, BMI and smoking, the GDM effect was no longer significant (OR = 1.04, CI: (0.87, 1.24, P value > 0.05).

Adjusting for age, BMI and baseline values of lipid indices revealed no significant difference in mean changes of total cholesterol, triglyceride, HDL-c and LDL-c between groups. Data indicated that overtime the trend of lipid parameters changed and the probability of progressing dyslipidemia was not significantly different in women with and without prior history of GDM (Figure 3).

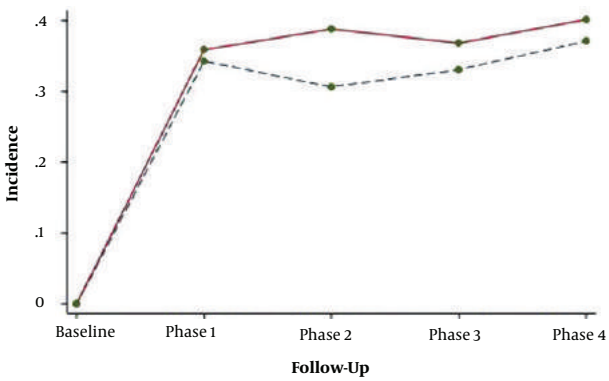

Figure 3. Probability pattern of dyslipidemia incidence within follow-ups. - - -: Non-gestational diabetes mellitus group; ___: Gestational diabetes mellitus group

We found that despite the non-significant trend of mean changes between groups, overall lipid profiles of the patients were worse than healthy women within follow-ups. Moreover, the impact of GDM on dyslipidemia disappeared when other covariates were added to the model, which may highlight the major effect of variables like BMI or smoking on lipid dysfunction in comparison with the GDM per se.

3.7. Hypertension After Hypertensive Pregnancy Disorders (HPD)

Hypertensive pregnancy disorders are defined as the onset of hypertension (HTN) with or without proteinuria after 20 weeks' gestation. In TLGS, hypertensive pregnancy disorders history was evaluated every 3 years based on self-reports through face-to-face interviews, any controversial data was corrected using their medical documents. According to the JNC-VI criteria chronic hypertension was defined as mean systolic blood pressure $\geq$ 140 mm Hg, mean systolic blood pressure $\geq$ 90 mm Hg or current use of antihypertensive medication (40). While hypertension and proteinuria associated with preeclampsia generally resolve soon after delivery, several studies have been demonstrated increased risk of future CVD especially HTN in affected women (41). We found that HPD are significantly associated with subsequent hypertension. At the end of a follow up, the cumulative incidences of hypertension in women with prior HPD was significantly higher than their age- and BMI matched controls (41.4 vs 19.5% for HTN). Women with prior of hypertensive disorders, compared to age- and BMI matched controls without HPD had a 2-fold increased risk for hypertension (95% CI: 1.4 - 3.2) (42).

We have also assessed future hypertension incidence and trend of blood pressure changes after 15 years follow-up in women with and without previous preeclampsia (PE). In agreement with findings of previous studies, results of these published data revealed that women with prior PE have a higher rate of hypertension progression compared to the non-PE one; mean changes of blood pressure differed significantly in the preeclampsia group compared without PE, after adjustment for potential variable. These findings could help policy makers and health care providers to manage women with a history of HPD, who are at risk for development of hypertension.

3.8. Androgen Excess Disorders; Insight from TLGS

3.8.1. Hirsutism

The absence of anovulation and/or hyperandrogenemia and the presence of terminal hair in females in a male-like pattern, is considered as idiopathic hirsutism (IH) (43). In TLGS, data regarding hirsutism was collected by a standard questionnaire and hirsutism was evaluated using the modified Ferriman-Gallwey (mFG) scoring and was diagnosed as m FG $\geq$ 8. The estimated prevalence of IH was 13.0% (95% CI: 10.9% - 15.1%) in participants of TLGS (44). Hirsutism is an important clinical sign of hyperandrogenism. It potentially influences the perception of a woman regarding her femininity and decreasing her self-esteem and leading to a reduction in the quality of life. Hence, we investigated the concordance between the patient's self assumptions of hirsutism with clinical diagnosis and noted the chin area to be the most concordant site in predicting the

women feelings of hirsutism. However, mFG system is still difficult to use in the clinical evaluation. Using population based data collected in the TLGS enables us to simplify mFG from 8 points to 3 (lip, abdomen and thighs); this subset had optimum sensitivity and specificity (91.5% and 92%, respectively) and a positive predictive value (PPV) of 72.2% and concordance percentage (91.9%), in comparison to original mFG score (45).

Results of TLGS study showed that among 12 androgenic sensitive body areas, the chin and skin had the highest area under curve of (0.81; CI; 0.78 - 0.84).

Despite the heavy burden of idiopathic hirsutism and its influence on the quality of life wellbeing of women, and its metabolic and cardiovascular consequences have not yet been clarified; TLGS is the first population based study that provides reliable information on this issue. Our findings demonstrate that the age and BMI adjusted prevalence of metabolic syndrome and insulin resistance (IR) was comparable in women with and without IH (30% vs. 23.9 and 25.7% vs. 22.5%, respectively).

3.8.2. Menstrual Cycle Irregularity and Cardio-Metabolic Disturbance

The menstrual cycles of all reproductive age participants of TLGS were assessed in detail from initiation of the study and re-checked in further phases of the study using structured questionnaires, valuable information which enables us to evaluate the impact of menstrual cycle irregularity on cardio-metabolic disturbances. So, TLGS as a long term prospective study, let us to assess the risk of metabolic disturbances in women with a history of menstrual irregularity.

It is revealed that women with history of menstrual irregularity had an increased risk for diabetes mellitus type 2 (DM2) (age adjusted HR: 2.01; CI: 1.59 - 3.50), which remained significant after the adjustment for BMI, FBS, parity and family history of diabetes (HR, 1.73; 95% CI: 1.14 - 2.64).

In addition, the results showed that menstrual irregularity was associated with prediabetes after adjustment for confounders (HR, 1.33; 95% CI: 1.05 - 1.69) (46).

Irregular menstrual cycles as one of the important components of PCOS, might be related to diabetes and cardiovascular diseases (47). A cohort study showed that the improvement of ovulatory cycles in PCOS patients could reduce in their risk for CVD and MetS (48). As a result our study revealed that a history of irregular menstrual cycles may be considered as a risk factor for development of DM and pre-DM, suggesting a comprehensive screening program and advocating healthy lifestyles in this group of women.

3.8.3. Polycystic Ovary Syndrome (PCOS)

PCOS is a heterogeneous disorder may leade to reproductive and metabolic disturbances. In TLGS, women aged, 15 - 49 years, were precisely screened for PCOS using validated questionnaire covering data on demographic characteristics, and reproductive, obstetrics and gynecological history, with emphasis on regularity of menstrual cycle, hyperandrogenic symptoms, and family history of irregular menstrual cycles, physical exams and biochemical/hormonal assessments. In TLGS, menstrual cycle irregularities due to oligo-ovulation or on-ovulation and either biochemical or clinical hyperandrogenism, were accessed after exclusion of other hyperandrogenism related disorders such as hyperprolactinemia and thyroid or adrenal disorders. As a result the prevalence of PCOS among reproductive age participants of TLGS was 8.5% (95% CI: 6.8% - 10.2%) (44) defined according to NIH criteria.

3.9. PCOS and Cardio-Metabolic Disorders: Insights from the Tehran Lipid and Glucose Study

The association between CVD outcomes and PCOS is still controversial. While some studies showed significant differences in CVD outcomes between PCOS and healthy controls, others resulted that there is no association between them. It is suggested that traditional cardiovascular/metabolic risk factors including insulin resistance, impaired fasting glucose, central obesity, dyslipidemia and hypertension, more common among women with PCOS in the general female population, are related to higher risk of mortality and morbidity (49). A meta-analysis revealed that PCOS patients had higher prevalence of impaired glucose tolerance, diabetes and MetS in both BMI and non-BMI matched studies (50). Nevertheless, most of this evidence was derived from clinical-based settings studies which did not included the milder PCOS phenotypes or their results did not compare with healthy controls with short length of follow up time.

Despite much literature available on prevalence, there are limited studies addressing the incidence of cardiometabolic risk factors in PCOS population. TLGS, a large prospective population-based study gives us the opportunity to compare the trend as well as incidence and hazard ratio of cardio-metabolic risk factors among this population and healthy controls.

In this respect, trend of cardio-metabolic risk factors showed that there were no statistically significant differences between mean changes of cardio metabolic feature

including waist circumference, lipid, blood pressure and sugar profiles. While triglyceride was elevated in the high BMI subgroup of women with PCOS, it reduced over time in both subgroups of non-PCOS women. The overall odd of insulin resistance in women with PCOS was more than threefold (95% CI: 1.3 - 8.9) higher that of the controls. In addition, the odds of IR reduced by 11% (95% CI: 2% - 19%) per year in PCOS, compared with healthy women.

In is concluded that while the insulin level and IR prevalence were higher in reproductive-aged PCOS patients compared to healthy one, the difference of these risk factors dilluted overtime. Thus, we concluded that the metabolic disturbances of women with PCOS in later life may be lower than those initially anticipated (48).

In addition, incidence rate and hazard ratios were estimatyed separately for those $\leq$ 40 years and $>$ 40 years for diabetes and pre-diabetes, based on extended cox proportional hazards regression model with age scale. Incidence per 1000 person years of diabetes in PCOS and healthy women was (12.9 per 1000 person years, 95% CI (8.4 - 19.7)) and (4.9 per 1000 person years, 95% CI (3.9 - 6.2), respectively. Also, the incidence rate of diabetes per 1000 person years (95% CI) among $\leq$ 40 years women with PCOS and healthy subjects were 13.4 (8.6 - 20.8) and 4.2 (3.2 - 5.4) respectively.

The incidence per 1000 person years of pre-diabetes in PCOS and healthy women was (29.7 per 1000 person years, 95% CI (21.5 - 41)) and (25.9 per 1000 person years, 95% CI (23.2 - 29) respectively. the incidence rate of diabetes per 1000 person years (95% CI) among $\leq$ 40 years women with PCOS and healthy subjects were 13.4 (8.6 - 20.8) and 4.2 (3.2 - 5.4) respectively. The incidence rate of pre-DM per 1000 person years (95% CI) among $\leq$ 40 years women with PCOS and healthy subjects were 29.7 (21.5 - 41) and 25.9 (23.2 - 29), respectively.

The incidence rates of hypertension, metabolic-syndrome, dyslipidemia and obesity were 13.9, 21.0, 46.1, 24.6, 50.6 and 13.8, 22.7, 46.0, 24.0 per 1000 person-years for PCOS and controls, respectively. Women with PCOS, aged $\leq$ 40 years had an adjusted higher risk of developing hypertension and metabolic-syndrome (HR: 2.08; 95% CI, 1 - 3.9; P $<$ 0.026) and (HR1.81; 95% CI, 1.1 - 2.9; P $<$ 0.019), respectively), a risk which however disappeared after the age of 40 year (in press).

The incidence and risk of cardio-metabolic outcomes were higher than in the general healthy women, although these risks diluted in the late reproductive period; women with PCOS may not be at additional risk for cardio-metabolic outcomes than the non-POCS population, suggesting that in prevention strategies, routine screening for diabetes may not be reinforced for PCOS patients at late reproductive ages if they had not been glucose intolerant during this period.

4. Conclusions

The population based nature of TLGS provides a unique opportunity for valid assessment of reproductive issues, the results of which could provide new information for modification of existing guidelines. Using valid tools for assessment of various aspects of reproductive history including structured questionnaire, comprehensive physical exams, meticulous checking of previous medical history and hospital records and standard validated biochemical and hormonal assessments were the main strengths of study facilitating a reliable results. However, relying on self-reporting for assessment of some aspects of reproductive histories such as contraceptive use and obstetrics characteristics could be a potential limitation in our study.

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Footnote

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Contributions and Implications of the Tehran Lipid and Glucose Study

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Abstract

Tehran Lipid and Glucose Study (TLGS), an epidemiological study of non-communicable disease with 20 years follow up in a developing country in nutrition transition is a unique study in 15000 family based individuals, 3 - 75 years of age in a part of large city of Tehran. The success rate of recruitment for 20 years, intervention for lifestyle change, and thyroid, reproduction and cardiometabolic genetic studies derived from TLGS have paved suitable path towards precision medicine. In this review, baseline findings and changes of risk factors for the development of NCD including body weight, nutrition, physical activity, blood pressure, tobacco smoking, serum glucose and serum lipids as well as metabolic syndrome, chronic kidney disease, quality of life and biochemical findings in TLGS cohort have been summarized. The results of community based intervention for lifestyle change caused decreases in the prevalence of metabolic syndrome and the incidence of diabetes. It is concluded that TLGS has served as a model for other cohort studies in Iran and the region; it has helped to mobilize scientists in developing countries; it has established locally needed definitions of NCD variables; has served as a model for cohort studies in developing countries in nutrition transition with all socioeconomic constraints and has helped manpower education and development of local CVD risk scores for implementation of NCD management.

Keywords: Tehran Lipid and Glucose Study, Non-Communicable Disease, Iran

1. Introduction

The landmark Framingham Heart Study, planned in 1947 and its initial design paper was published in 1951 (1), was an important turning point in our evolving understanding of non-communicable diseases (NCD) in last century. Although the standardized measurement of risk factors of NCD and follow up in Framingham served as an important precedent for future cohort studies in developed countries (2), there have been a paucity of prospective investigation of the epidemiology of NCD in the developing-low income countries.

The legacy of Tehran Lipid and Glucose Study (TLGS) is that it was planned in a developing country in nutrition transition (3) for investigation of epidemiology of NCD and has continued follow up of 20 years (4). Special characteristics of TLGS could be summarized as follows:

1. Most NCD cohort studies have been performed on adult population. Framingham Heart Study recruited approximately 6000 adults, while TLGS consists if a cohort of 15000 family based individuals from 3 to 79 years of age (5).

2. Those cohort studies performed in a population of small city, such as Framingham may have operational advantages, in particular in collection of outcome data. TLGS has population of approximately 8.5 million. Therefore, collection of outcome data from over 170 hospitals and moving of participants to different part of the city have made obstacles in management of the study.

3. The design of TLGS composed of collection of baseline data in 3 years and community lifestyle intervention for prevention of NCD in one third of study population, followed by re-collection of data every 3 years. Interventional studies carry special difficulties that observational studies do not have (6).

4. Executing a cohort study in developing country faces inadequacy in infrastructure of communication, social determinants, education, health structure and many related factors, which need special planning.

5. The success of recruiting 72.9% (Figure 1) of original cohort after nearly 2 decades has been mainly due to an expert team of social workers, with close connection to each family in the area of study.

6. The addition of Tehran Thyroid Study, Reproduction Study, Cardiometabolic Genetic Study in the population of TLGS had prepared ground for more extensive cross-

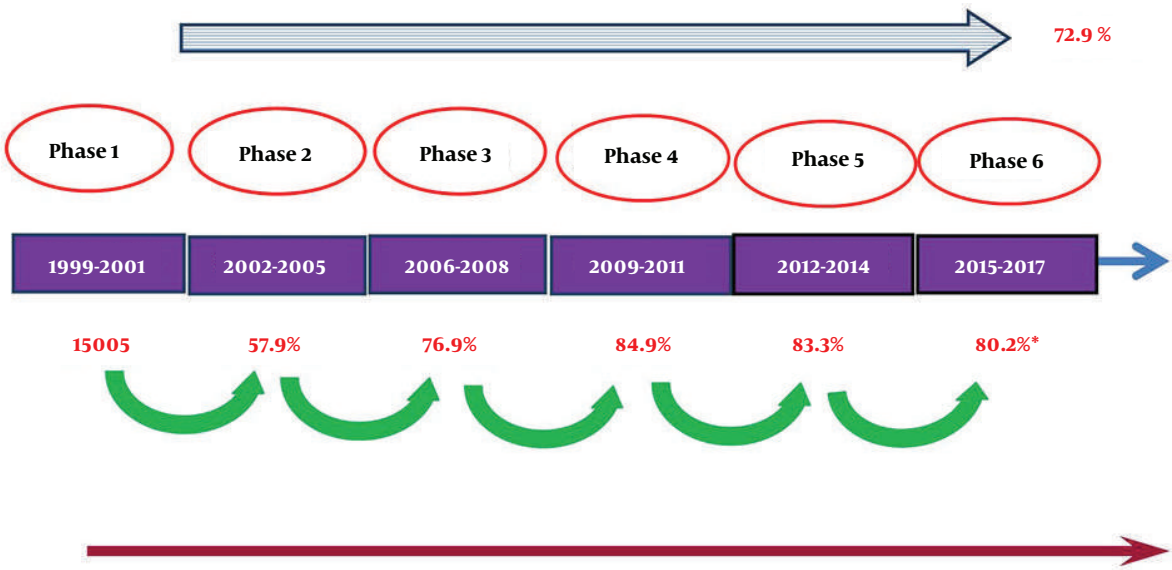

Figure 1. Design of Tehran Lipid and Glucose Study. Each phase lasted 3 years. 72.9% of the original cohort have participated in phase 6 (18 years of follow up). * Denotes percent of participation from previous phase.

specialty investigations, paving suitable path towards precision medicine.

Main outcome and implications of TLGS consist of factors of investigating risk in the development of NCD, effect of community lifestyle intervention, and findings from concomitant study in the thyroid, reproductive and genetic domain.

2. Factors of Risk in the Development of NCD

The concept of risk factors was first developed by Kannel et al. in 1961 describing the six-year follow up in the Framingham Heart Study (7). TLGS was the first to show the systemic and standardized follow up of NCD risk factors in a community in nutrition transition in a developing country (8). Figure 2 demonstrates steady increase in BMI, waist circumference, blood pressure, and percent of obesity in TLGS. Trends of NCD risk factors in the first 20 years of TLGS have been described in previous papers (9-24). Main findings have been included in Figures 2 and 3.

2.1. Body Weight

Prevalence of overweight and obesity which was 20.8 and 63.6% in 3 - 19 years age and adults respectively has increased in both young and adult population. The crude prevalence of obesity and abdominal obesity in adults has increased from 23.1 and 47.9% at baseline to 34.1 and 71.1% at the end of follow up, respectively. Relative risk of obesity was 1.62 (1.49 - 1.76) for men and 1.24 (1.19 - 1.29) for women. Relative risk for abdominal obesity was 1.46 (1.41 - 1.52) and 1.22 (1.18 - 1.27) in men and women, respectively (9).

In the TLGS, 2.0 and 7.7% of the adult population wee metabolically healthy obese (MHO) in total and obese population, respectively. Corresponding numbers for metabolically healthy but abdominal obese (MHAO) were 12.4 and 23.5% respectively. These two phenotypes were unstable conditions and nearly half of the individuals developed metabolic risks during follow-up. At follow up MHAO, but not MHO phenotype showed and increased risk of CVD compared to metabolically healthy non-abdominal obese individuals (25-27).

2.2. Nutrition

Consummation of whole grains, legumes, nuts and healthy dietary pattern reduced and consumption of white rice, salty/weet snacks increase risk of MetS. Higher adherence to healthy food choices were also associated with reduced odds of MetS, obesity, dyslipidemia and pattern. The western dietary pattern increased the association of polymorphism with MetS (10, 28-30).

Follow up studies showed that dietary pattern of two-third of participants was not in accordance with dietary recommendations. Higher dietary scores of variety and healthy dietary patterns were associated with reduced odds of dysglycemia (31-33).

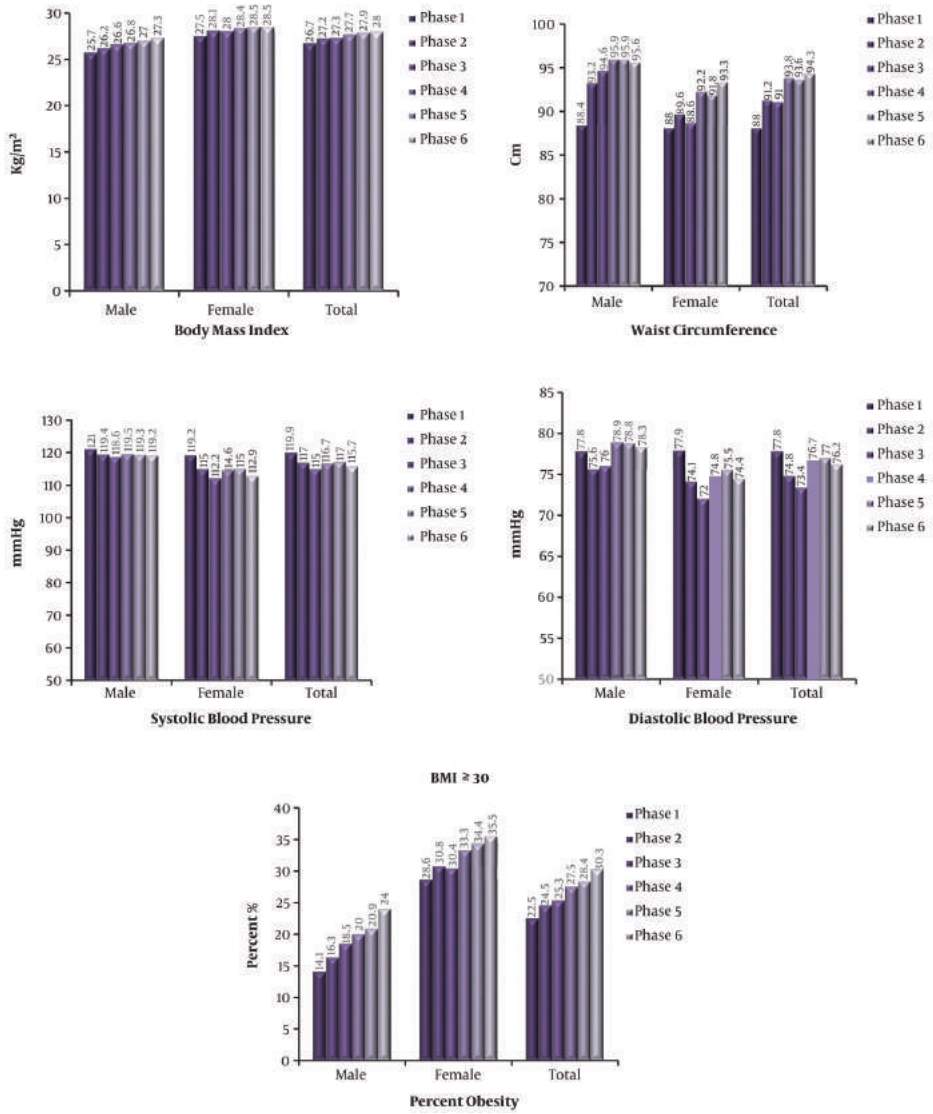

Figure 2. Mean body mass index (BMI), waist circumference (WC), systolic and diastolic blood pressure and percent obesity (BMI $\geq$ 30 kg/m^2) during 6 phases of the Tehran Lipid and Glucose Study. Each phase lasted 3 years. There have been increases in BMI, WC, diastolic BP and percent obesity during 18 years of follow up.

2.3. Physical Activity

At baseline, low physical activity was present in 69.8% with little change in the follow-up. The prevalence of physical inactivity increased with rise in BMI: 69.8% of overweight and 75.3% of obese men had low physical activity, with higher risk of metabolic syndrome, systolic blood pressure and elevated serum triglyceride (11-34).

2.4. Blood Pressure

The prevalence of hypertension was 23%. Crude incidence rate was 33.6 per 1000 person-years. Age, baseline systolic BP and BMI, and baseline diastolic BP and waist circumference were important risk factors for isolated systolic and diastolic hypertension, respectively. Hypertension was associated with increased CVD, CVA and all cause mortality (12, 35, 36).

2.5. Tobacco Smoking

The prevalence of tobacco smoking increased from 25.5 to 35.4% in men and from 3.4 to 6.8% in women during 10 years follow-up. Water- pipe use in youth also increased. Increased risk of combined IFG/IGT, hypertension and CVD in men and increase risk of chronic kidney disease in women

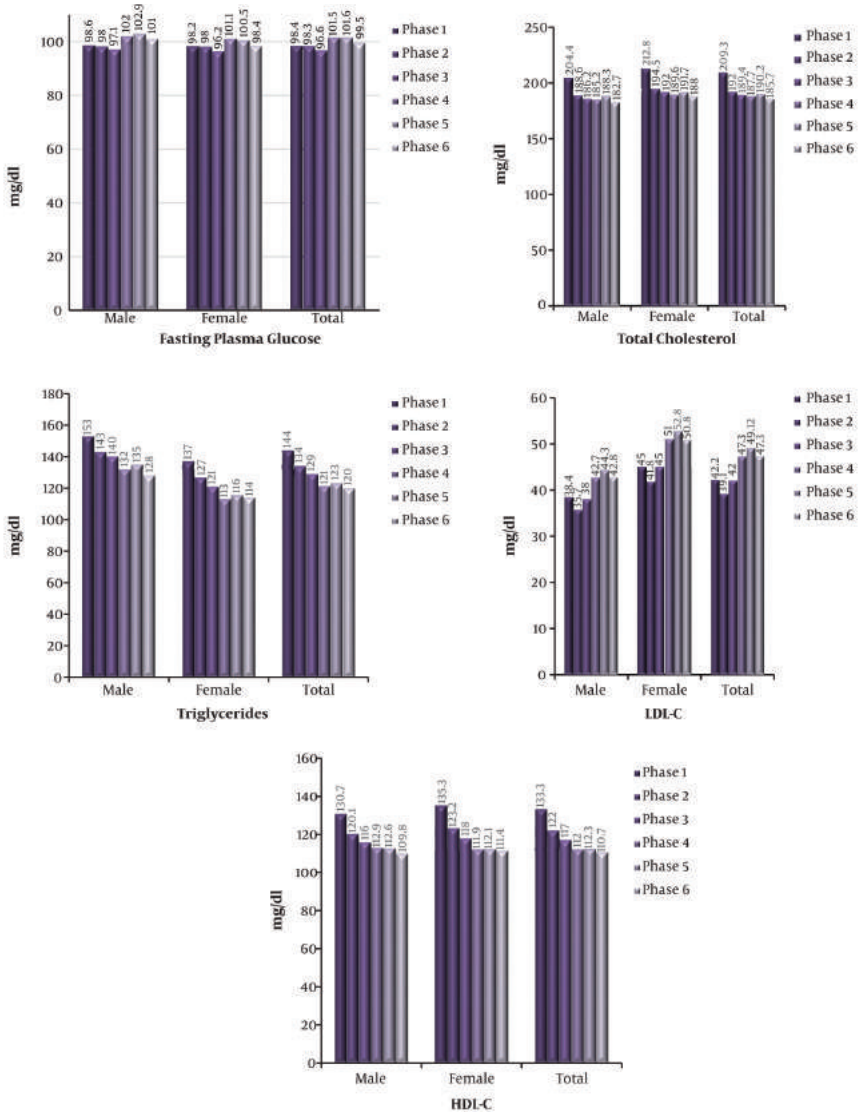

Figure 3. Mean serum concentrations of glucose and lipid profile during 6 phases of the Tehran Lipid and Glucose Study. Each phase lasted 3 years. There have been decreases in serum total cholesterol, triglycerides and LDL-C and increase in serum HDL-C, with no significant change in FPG.

smoker was shown (11), smoking contributed to 7.7% of all cause mortality with HR 1.75 (36).

2.6. Serum Glucose

At baseline the prevalence of diabetes was 13.2 and 14.7% in adult men and women, respectively. Incidence rate of diabetes in adults was 10 per 1000 person-year, and that of prediabetes was 36.3 per 1000 person-year. Diabetes was significantly associated with increased risk of CVD and death. Hyperinsulinemia, serum 25-OH vitamin D, alanin aminotraferase and waist circumference provided additional prognostic information beyond the traditional risk factors incident diabetes (14, 36, 37).

2.7. Serum Lipids

The baseline prevalence of low HDL-C and high LDL-C among adolescents was 14 and 17%, respectively (38). Corresponding figures for adults were 19 and 28%, respectively (39). Serum total cholesterol and triglycerides were significantly higher in men than women and increase by advancing age in both genders. During over a decade follow up, significant decrease in serum concentrations of total cholesterol, triglycerides and LDL-C and increase in serum HDL-C occurred in both gender (40). Results

were unchanged after excluding participants with prevalent CVD and those using lipid lowering medications: 1.5 and 3.7% at baseline and 9.0 and 11.4% after follow up in men and women, respectively. Therefore, some important part of correction of dyslipidemia was attributed to national program of changing solid oil to liquid oil production throughout the country in last decade of last century by the government (15).

3. Related Findings to NCD

3.1. Metabolic Syndrome

Based on ATP III definition, the prevalence was 30.1% at baseline, 42% in women and 24% in men (41). The most prevalent metabolic abnormality was low-HDL. The incidence rate of metabolic syndrome was 551/10000 person/year. In adolescents the prevalence was 10.1%. metabolic syndrome was a significant predictor of total and cardiovascular mortality in both gender (16-42).

3.2. Chronic Kidney Disease

The prevalence of CKD was 11.3 and 8.5% by 2 different definitions (43). The incident rates were 285 and 233 per 10000 person-years for women and men, respectively. Elevated waist circumference and waist gain were associated with increase incidence of CKD. In lean individuals, CKD was an indefindent predictor of CHD and stroke (17).

3.3. Quality of Life

Metabolic syndrome was associated with poor physical quality of life in women, particularly in those who had more components of metabolic syndrome. Only reproductive age women with metabolic syndrome were more likely to report poor physical component summary subset of short form health survey (18).

3.4. Biochemical Findings

In addition to FBS, GTT, serum lipids and lipoprotences, measurement of many biochemicals have been performed in TLGS. C-reactive protein, interluekine-6 and homocysteine were found to be associated with NCDs. Levels of CRP and IL-6 was higher in subjects with abdominal obesity, as compared to normal weight individuals (19).

In Addition, circulating nitric oxide metabolites (NO_x) was associated with the risk and could predict NCD. Findings suggested that NO_3/NO_2 exposure from usual diets may contribute to development of NCDs (20).

3.5. Tehran Thyroid Study

Thyroid study began in 5920 adults of TLGS and the design was published in 2013 (44). This study aimed to investigate the gap in knowledge regarding epidemiology of thyroid disorders and systematic evaluation of trend of thyroid hormones, TSH and thyroid antibodies in a population over time period. So far, it has defined the reference ranges of fT4, TSH and thyroid peroxidase antibody (TPOAb). The rate of persistent euthyroidism has been 93% and the incidence rate of thyroid disorders was estimated at 21 per 1000 person-year. Serum fT4 had negative association with insulin resistance in all and positive association with blood pressure only in men. No relation between various thyroid status and the prevalence and incidence of CVD was detected (21).

3.6. Reproductive Studies

A decrease in age of menarche from 14 to 13 years was observed during 6 decades. There was no specific trend in menopausal age. Findings showed good agreement between serum anti-mulerian hormone and predicted age of menopause (45). Prevalence of infertility was 17.3%. Prevalence of PCOS and idiopathic hirsutism was 8.5 and 13.0%, respectively. Significant association between PCOS with increased hazard of diabetes, prediabetes and risk of developing metabolic syndrome was observed only in women aged $\leq$ 40 years (22).

3.7. Genetic Studies

The association between variations in 26 genes were studied in 6 phenotypes and complex 17 trials. 47 variants were associated with NCDs and related traits (23). Extra-indivuals and pedigrees have been collected during follow-up time and the data of genome wide studies are under analysis.

3.8. Life Style Intervention

A community-based intervention for life style modification was adapted following baseline data collection in TLGS. It was planned to educate trainers from the community, followed by supervision and evaluation from TLGS team. Educational interventions were performed by family-based, community based and school-based programs (6).

Baseline data of TLGS had shown higher prevalence of NCD risk factors compared to Western and Asia-Pacific countries. However, mild indirect interventions showed a decrease in the prevalence of metabolic syndrome and the incidence of diabetes and prediabetes. After 3.6 years of interventions, the incidence of diabetes was decreased by 65% (24, 46, 47).

Table 1. Approximate Costs of Survey for Each Participant Per Year: Tehran Lipid and Glucose Study

Item	Expenditure	
	Rials	Euro[a]
History, physical exam and questionnaires	60,000	1.2
Elecrocardiogram	40,000	0.8
Laboratory measurements	70,000	1.4
Manegerial services and other costs	830,000	16.6
Total	1,000,000	20.0

[a] Exchange rate has varied during last 20 years, 5000 Rials per each Euro has been estimated as an average.

4. TLGS as a Model for Other Cohort Studies

Tehran Lipid and Glucose Study was the first prospective 20 year cohort study in West-Asia and Eastern Mediterranean region. Table 1 shows low survey cost of only 1,000,000 Rials (20 Euro) for each participant of TLGS per year of study. The success of TLGS, with over 500 peer-reviewed Journal publications, motivated the establishment of many cohort studies in the region, in the past decade. In the Islamic Republic of Iran over 20 cohort studies have developed and a Concersium of Iranian Cohort has been formed. In 2018, approximately 150,000 people have entered Iranian cohort studies (48). These cohort studies will continue TLGS path to use standardized protocol for measurement of risk factors and outcomes of NCD's, to employ repeated examinations over time for detecting the progression of risk factors and to use multivariate analysis to disclose the independent contributions of multiple risk factors in NCDs.

5. Contributions and Future Prospective

Findings of TLGS, a 20 year long prospective study of NCDs in a developing country has produced many important lessons from this well controlled epidemiological investigation over the past 2 decades. The main lessons gained by TLGS have been (1) to mobilize scientists in countries other than developped ones to establish prospective cohort studies for assessment of risk factors of NCDs in their region, to correct many clinical misconceptions, to establish the impact of risk factors and the importance of multivariable risk factors influencing NCDs; (2) to establish locally needed definitions of variables; for example cut-offs of waist circumference for Iranians; (3) to show that with good management, complex cohort studies could be implemented in a rapidly growing country on nutrition transition; (4) to demonstrate that training the trainers in a community with minimal expenses could be effective in reducing incidence of diabetes, prediabets and metabolic syndrome; (5) to show that in situations with constraint budgets, with rising enthusiasm in dedicated researchers and personals, much sciences could be gained in health system research; (6) to announce unhealthy diet and poor physical activity of the community and to propose ways of change in lifestyle to the health authority; (7) to develop ways of exchange of knowledge in order to propagate findings to medical personnels and general population; to determine appropriate technological advances in molecular medicine and new interventional tools in population research in less developed countries. (8) to develop CVD risk scores based on data from local population and implement the formula in nationwide NCD management (IRA-PEN).

In recent years, the legacy of TLGS continues with genomic study including genom-wide study of TLGS participants, plans for metabolomic studies, more development of research in epigenetic domain and wider collaborations with scientists in different fields of medicine for employing more creativity and newer investigation tools. In addition, the close collaboration with various departments of the Ministry of Health and Medical Education makes this study unique to offer prevention methods for control of NCDs in countries in nutrition transition. For the future, all data gathered in TLGS could help the development of precision medicine in the region.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

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This journal accepts only manuscripts through the online submission system. It is easy to use and easy to track, thus by conducting all steps electronically, your submission will be expedient. Contributors can submit via our website. Once you submit an article, it will be forwarded to one of the editors and afterwards to at least two peer-reviewers. The author will be notified of the submission process by means of E-mail.

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This letter should be uploaded online as a word file. The author should state that the manuscript has not been and will not be published or submitted elsewhere. The financial disclosure should be declared. The letter must include a statement declaring that the study complies with current ethical considerations. Authors reporting experimental studies on human subjects must include a statement of assurance in the Materials and Methods section of the manuscript reading that: (1) informed consent was obtained from each patient included in the study and (2) the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

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Use the font Times New Roman size 12 for the body, size 12 bold for subheadings, size 14 for headings, and size 14 bold for the title, Line spacing = Double.

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Meltzer PS, Kallioniemi A, Trent JM. Chromosome Alterations in Human Solid Tumors. In: Vogelstein B, Kinzler KW, editors. The Genetic Basis of Human Cancer. New York: McGraw-Hill; 2002. p. 93-113.

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