به نام خدا

MEN ١

questions

- what are the prevalence of MEN ١ components?
- What are the factors influencing the prevalence?
- Is there a genotype phenotype correlation?
- What are the difference between endocrine tumor in MEN ١ & sporadic tumors?
- What is the relationship between prolactinoma & weight gain in our patient?

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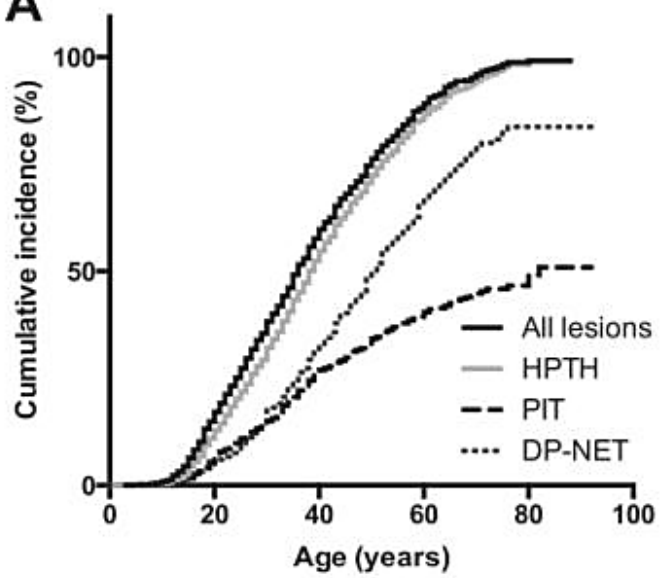
MEN۱ syndrome

autosomal dominant(۵۰% risk), high penetrance

A

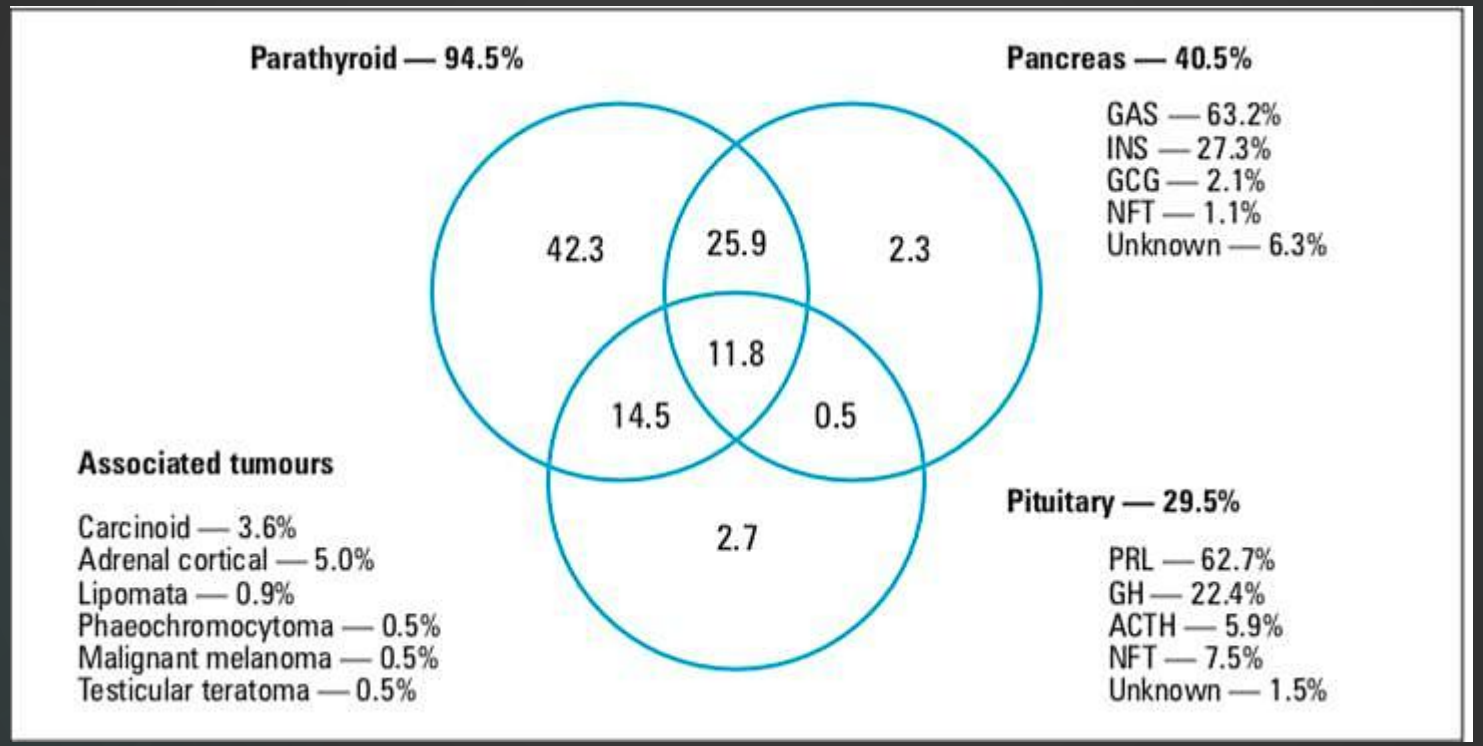


B

Age (years)	All lesions Penetrance (%)	All lesions uninjured patients (n)	HPTH Penetrance (%)	PIT Penetrance (%)	DP-NET Penetrance (%)	ADRE Penetrance (%)
5	0.1	1327	0.1	0,0	0,0	0.1
10	0.9	1294	0.4	0.1	0.5	0.1
20	17.1	1028	12.8	6.9	5.4	0.5
30	38.3	736	32.1	15.1	17.2	3.4
40	59.8	455	54.8	27.0	32.8	10.1
50	76.2	253	72.5	34.3	49.6	20.1
60	89.3	105	86.7	40.5	66.7	29.4
70	96.0	32	94.5	44.8	78.9	38.6
80	99.2	3	98.9	49.1	83.7	42.0

UMD-MEN۱ Database: An Overview of the ۳۷۰ MEN۱ Variants Present in ۱۶۷۶ Patients From the French Population. J Clin Endocrinol Metab,March۲۰۱۹،۱۰۴(۳):۷۵۳-۷۶۴

MEN ١ main features prevalence



Pituitary tumors in MEN١ syndrome- the new insight into the diagnosis and treatment.Endrkrynologia polska ٢٠١٩;٧٠(٥)

MEN1 syndrome

Table 1. Age-related penetrance by 50 years of age for "classical" MEN1-associated tumors[60,63].

MEN1-associated endocrine disorder	Age-related penetrance by 50 years of age
Primary hyperparathyroidism (multiglandular disease)	73–75%
Pituitary adenomas	31–48%
Islet cell tumors*	45–49%

Genetics of Multiple Endocrine Neoplasia type1 Syndrome :What's New and What's old. F1000Research 2017

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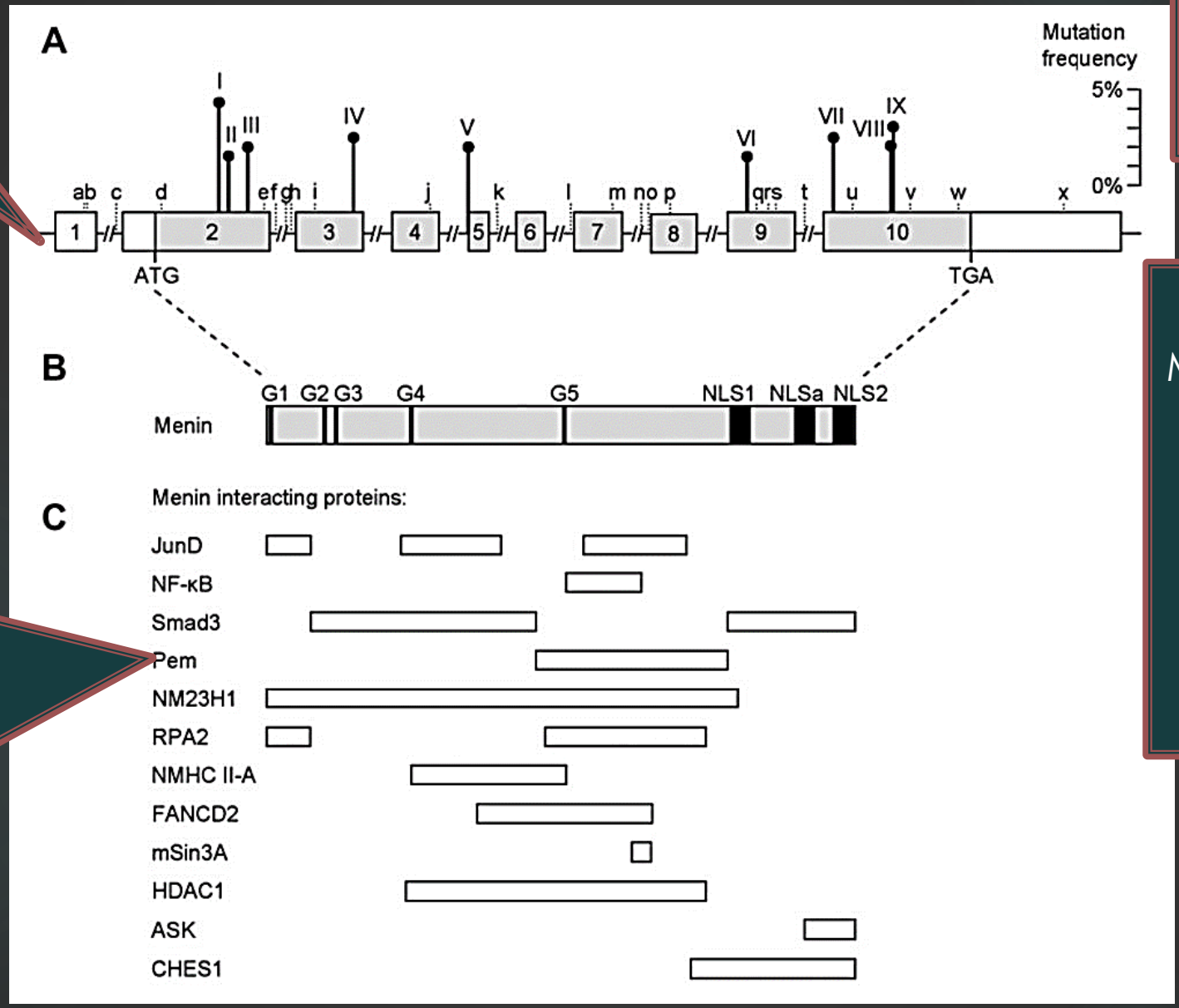
Chromosome ١١q ١٣
Tumor suppressor gen

Two-hits hypothesis mutation +LOH in unaffected allele



٦١٠ amino acid nuclear protein in non-dividing cells.
Transcription regulation ,proliferation
Genomic stability
DNA repair
Cell division/cycle

MEN١ mutation leads: Truncated pro lacking nuclear localization signals, reduced stability, enhance degradation.

Multiple endocrine neoplasia type 1,Best Practice & Research Clinical Endocrinology & Metabolism 24(2010)355-370

Mutation of MEN١ gene

- over ١٨٠٠ mutation
- ٤١% frameshift deletion/insertion
- ٢٣% nonsense mutation
- ٢٠% missense mutation
- ٩% splice site mutation
- ٦% in-frame deletion/insertion
- ١% whole/particular gene deletion
- ٥-١٠% have whole gene deletion mutation in noncoding region (promotor/untranslated)

Table 2. Different types of *MEN1* gene mutations reported in the literature and their frequencies[57].

Types of *MEN1* gene mutations	Percentage
Nonsense	23%
Frameshift deletions or insertions	41%
In-frame deletions or insertions	6%
Splice site	9%
Missense	20%
Whole gene or particular gene deletions	1%

Genetics of Multiple Endocrine Neoplasia type١ Syndrome :What's New and What's old. F١٠٠٠Research ٢٠١٧

Mutations at ٩ site in MEN١ gene accounts for over ٢٠% of all germ-line mutations

Table 3. The nine recurring mutations by type[55,56].

Type of *MEN1* mutations	Localization within the gene (there is more than one mutation in most of each of the following codons)
Deletions or insertions	Codon 83
	Codon 84
	Codon 120
	Codons 210–211
	Codons 514–516
Novel acceptor site	Intron 4
Nonsense	Arg98Stop
	Arg415Stop
	Arg460Stop

Genetics of Multiple Endocrine Neoplasia type1 Syndrome :What's New and What's old. F1000Research 2017

What to do when a MEN١ gene mutation is not detected at DNA sequencing?

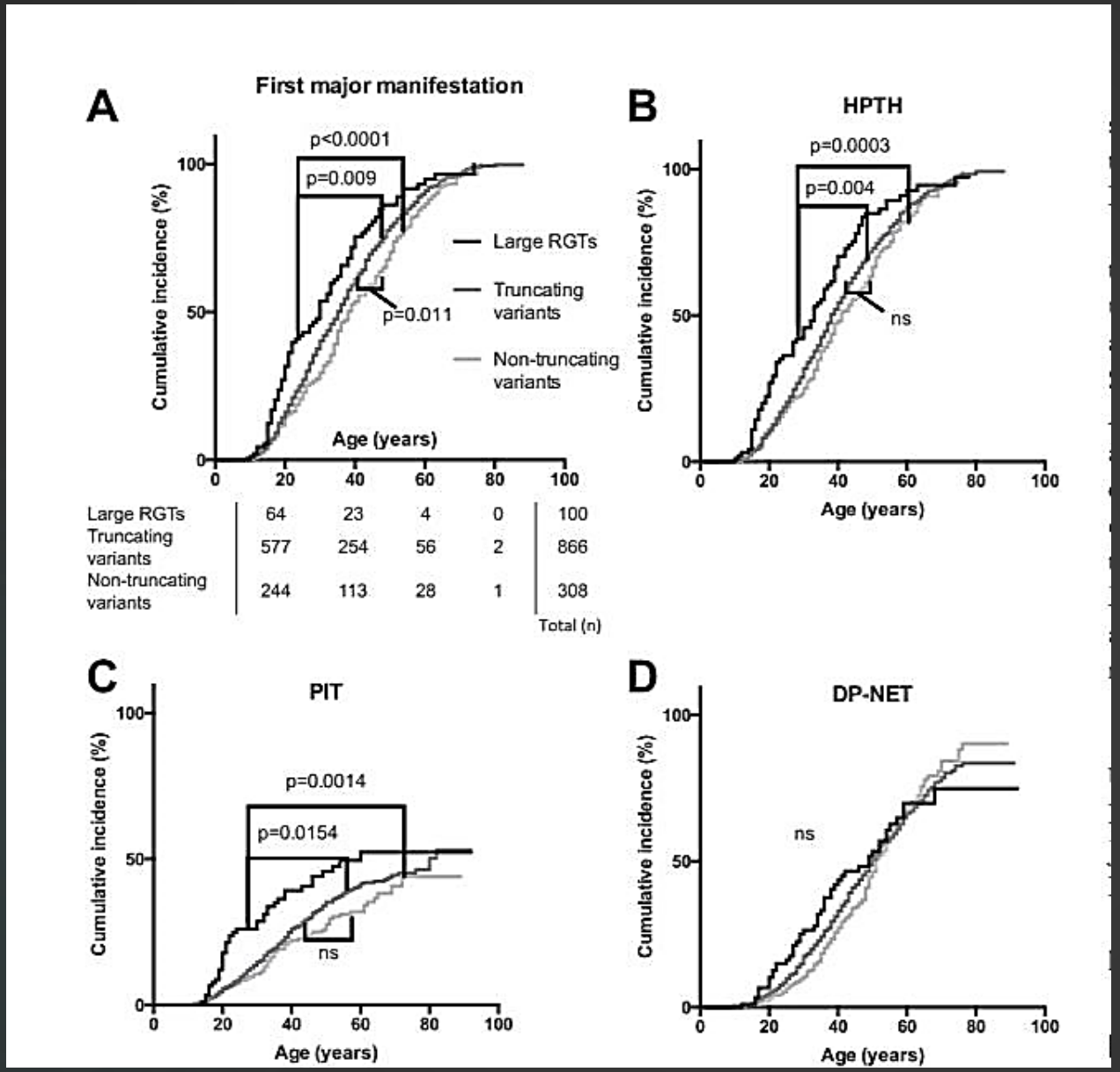
- ٥-١٠% of patient
- CGH (comparative genetic hybridization) or NGS(next generation sequencing) :detecting gross alteration at the MEN١ gene(large deletion,insertion,other large genomic rearrangements in MEN١ gene.
- MPLA (multiplex ligation-dependent probe amplification):detecting copy number change within a specific gene.
- In MEN١index case with negative sequencing MEN١ gene MPLA should be considered.
- CDKN١B

Genetics of Multiple Endocrine Neoplasia type1 Syndrome :What's New and What's old. F1000Research 2017

MEN ١ phenocopies:

- In families with classic MEN١ symptom & negative result for MEN١ or CDKN١B mutations further evaluation should contain:
  - CDKN١A
  - CDKN٢B
  - CDKN٢C
- They all negatively regulate cell cycle progression & cell growth.

Genetics of Multiple Endocrine Neoplasia type1 Syndrome :What's New and What's old. F1000Research 2017



UMD-MEN1 Database: An Overview of the 370 MEN1 Variants Present in 1676 Patients From the French Population. J Clin Endocrinol Metab,March2019,104(3):753-764

- Patients with MEN١ with large RGTs experienced earlier first MEN١ manifestation.
- HPTH, PIT developed at earlier age than in patients with truncating/ non truncating variants.
- Earlier molecular screening In family with large RGTS .
- In MEN ١ patients with truncating mutation the age of first manifestation is earlier than non truncating.

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Genotype phenotype correlation in MEN1

Table 2
Multiple endocrine neoplasia type 1–associated tumors in five unrelated families with a 4-bp deletion at codons 210 and 211.

Family	1	2	3	4	5
Tumors					
Parathyroid	+	+	+	+	+
Gastrinoma	+	−	+	+	+
Insulinoma	−	+	−	−	−
Glucagonoma	−	−	−	−	+
Prolactinoma	−	+	+	+	+
Carcinoid	+	−	−	−	−

+, presence; −, absence of tumors. Adapted from Ref. 2, © The Endocrine Society.

Multiple endocrine neoplasia type 1,Best Practice & Research Clinical Endocrinology & Metabolism 24(2010)355-370

Genotype phenotype correlation in MEN١

- MEN١ missense mutation & FIHP

  Nat Clin Pract Endocrinol Metab ٢٠٠٨

- Single Non sense mutation(R٤٦٠X) & prolactinoma,carcinoid,parathyroid tumor.

  *.J Clin Endocrinol Metab (*٢٠٠٩*)*

- Monoallelic ٥ kb deletion of genomic DNA involving promotor region MEN١ & exon ١،٢ & aggressive tumor behavior.

  *. Clin Endocrinol(*٢٠١١*)*

- Relapsing macro prolactinoma & menin & p٢٧ kip down-regulation.

  *. Endocr J (*٢٠١١*)*

- CDKN١B genetic variant & MEN١ related aggressive tumor.

  J Cell Mol Med(٢٠١٥)

- No correlation was found between disease age of onset ,distribution of PHPT ,pituitary tumor & MEN١ mutation type or localization.

  *Endocine(*٢٠١٨*)*

Any role for epigenetic and/or modifying genetic mechanisms in the clinical expression of MEN١?

- Epigenetic mechanisms triggered by environmental factors may influence the disease phenotype in patients carrying the same MEN١ mutations.
- CDKN١B variant(inactivating mutation in this gene cause MEN ٤) can be disease modifying in MEN ١ patients with truncating MEN١ mutation, causing higher MEN١ related tumors.

Genetics of Multiple Endocrine Neoplasia type1 Syndrome :What's New and What's old. F1000Research 2017

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Pituitary tumors in MEN١ syndrome

- Pituitary tumor is found in ١٥-٥٠% MEN١ patients
- First manifestation in ١٥% of sporadic form & less than ١٠% of familial form of MEN١
- Larger, more aggressive, resistant to conventional therapy
- ٨٥% are macro adenoma, in contrast with sporadic pituitary adenoma in witch ٤٢% of lesions are> ١cm.
- Treatment is the same as sporadic pituitary tumor:

  Prolactinoma : dopamine agonists ,TSS , radiotherapy

  GH,ACTH producing tumor :TSS

  Non-functional : TSS if treatment is indicated(visual disturbance, close proximity to optic chiasm or rapid growth)

Pituitary tumors in MEN1 syndrome- the new insight into the diagnosis and treatment.Endrkrynologia polska 2019;70(5)

Pituitary tumor in MEN۱

PRL(۴۰%)
GH(۲۵%)
ACTH(۵%)
Non functional

TABLE 4. Pituitary adenomas in MEN1 patients and in controls

	MEN 1 pituitary adenomas (n = 136)	Control (non-MEN1) pituitary adenomas (n = 110)	*P*
Age (yr)	38.0 ± 15.3	36.2 ± 14.6	NS
Mean follow-up (yr)	11.1 ± 8.7	10.0 ± 6.3	NS
Type of pituitary adenoma:			
PRL	n = 85	n = 68	NS
GH	n = 12	n = 15	
ACTH	n = 6	n = 7	
Cosecreting	n = 13	n = 2	
Nonsecreting	n = 20	n = 18	
Clinical signs related to tumor size	n = 39 (29%)	n = 15 (14%)	$P < 0.01$
Tumor size			
Microadenoma	n = 19 (14%)	n = 64 (58%)	$P < 0.001$
Macroadenoma	n = 116 (85%)	n = 46 (42%)	
	no data: n = 1 (1%)		
Outcome			
Normalization of pituitary hypersecretion	n = 49 (42%)	n = 83 (90%)	$P < 0.001$

For each qualitative data, the number of patients and the percentage of affected patients in each group (MEN1 patients and controls) are given. The results of the statistical comparison between the two groups (MEN1 patients and controls) are shown in the last column.

Pituitary Disease in MEN Type ۱: Data from the France-Belgium MEN۱ Multicenter Study. J Clin Endocrinol Metab,February ۲۰۰۲،۸۷(۲):۴۵۷-۴۶۵

Pituitary Tumors and Hyperplasia in Multiple Endocrine Neoplasia Type 1 Syndrome (MEN1): A Case-Control Study in a Series of 77 Patients Versus 2509 Non-MEN1 Patients

, Number 4, April 2008

ary Lesions in MEN1 and non-MEN1 Patients

Types of Lesions	MEN1 n (%)	Non-MEN1 n (%)	Fisher Exact Test *P*
Hyperplasia	3 (4)	0 (0)	< 0.0001
Multiple adenomas	3 (4)*	3 (0.1)†	
Single adenoma	71 (92)	2506 (99.9)	
Immunoprofile:			
Monohormonal	41 (58)	1780 (71)	0.004
Plurihormonal	28 (39)‡	560 (22)	
Nonimmuno-reactive	2 (3)	166 (7)	
Functional status			
Functional	51 (72)	1599 (64)	0.21
Nonfunctional	20 (28)	907 (36)	

*1 triple PRL, 2 ACTH/PRL.
†3 ACTH/PRL.
‡Cells contributing the most to χ^2 association.

Am J Surg Pathol.2008;32(4):534-543

TABLE 5. High Percentage of Ki-67 Labeling (>3%) and Histologic Invasion in MEN1 Tumors and Non-MEN1 Control Subgroup According to Tumor Size

	Grade I	Grade II	Grade III	Grade IV	Total
Ki-67 > 3%					
MEN1 tumors	1/7	6/20	1/12	2/8	10/47 (21.3%) ns
Non-MEN1 tumors	11/60	8/53	13/84	2/12	34/222 (15.5%) ns
Histologic invasion					
MEN1 tumors	2/13	2/10	4/6	2/3	10/32 (31.3%)*
Non-MEN1 tumors	2/87	5/62	17/58	6/6	30/213 (14.0%)*

*$P < 0.05$.

Am J Surg Pathol.2008;32(4):534-543

ORIGINAL ARTICLE

Long-Term Natural Course of Pituitary Tumors in Patients With MEN1: Results From the DutchMEN1 Study Group (DMSG)

Joanne M.
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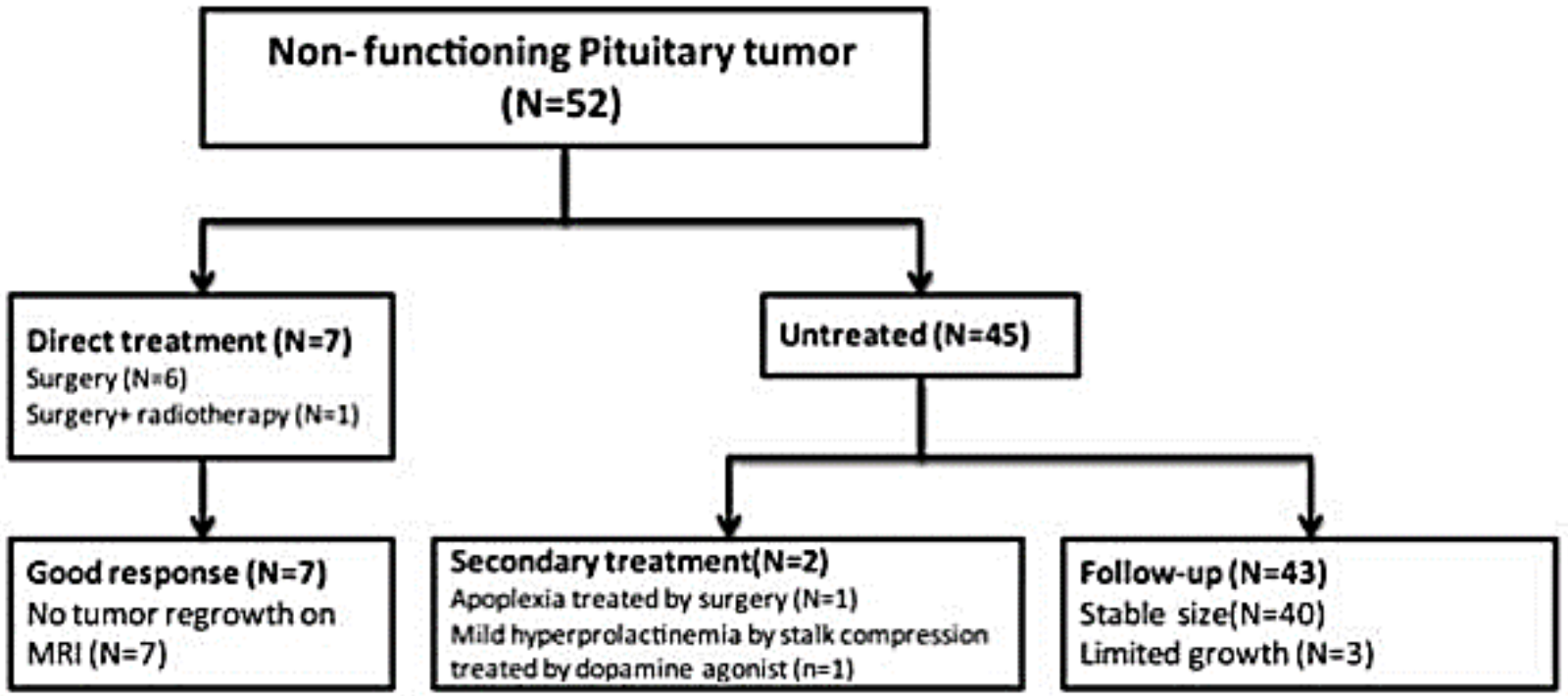

Figure 2. Flowchart of treatment and outcomes for nonfunctioning pituitary tumors.

J Clin Endocrinol Metab.۲۰۱۵

Long-Term Natural Course of Pituitary Tumors in Patients With MEN1: Results From the DutchMEN1 Study Group (DMSG)

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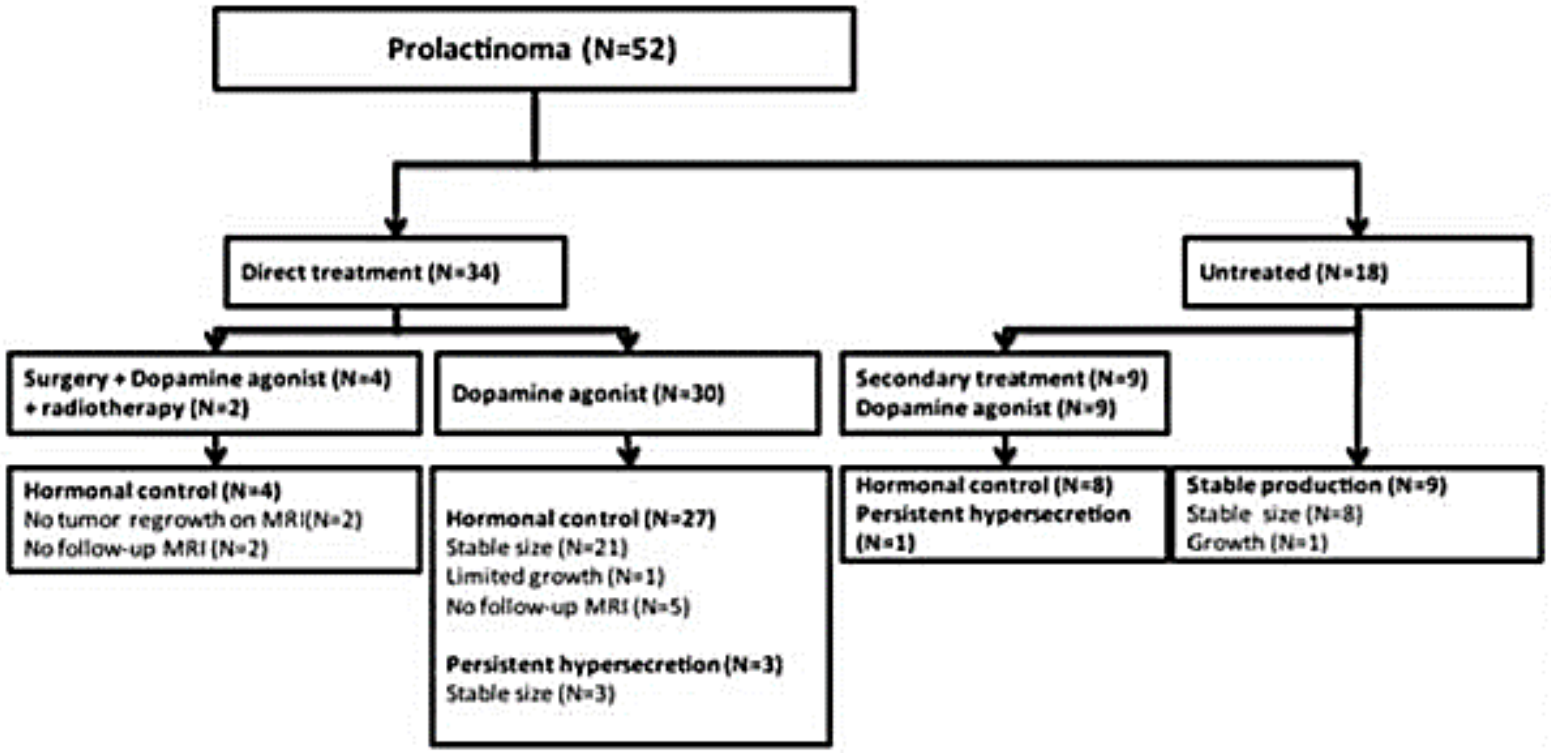

Figure 3. Flowchart of treatment and outcomes for prolactinoma.

J Clin Endocrinol Metab.2015

PIT in MEN1

- Screening for PITs in MEN1 patient resulted in detection microadenomas with relatively indolent behavior.
- Growth of nonfunctioning microadenoma was detected occasionally after many years without clinical consequences.
- Treatment & f/u MEN1 associated PIT should not be different from sporadically occurring PIT.

hyperparathyroidism

- Parathyroid hyperplasia/adenoma
- Most common & often earliest endocrine manifestation in MEN١ ,١٠٠% penetrance by the age of ٥٠.
- Compared to sporadic PHPT:

  earlier age(٢٠-٢٥ age vs ٥٥ years)

  Multiple gland involvement(٨٠-٨٥% of sporadic PHPT have single gland disease).limited value of preoperative localizing imaging ,bilateral neck exploration

  Greater decline in BMD

  High recurrence rate after surgery(٥٠% in ١٢ years)

  Decreased BMD recovery in lumbar spine,femur,١/٣ distal radius.

TABLE 2. Clinical Characteristics of Patients With MEN1 and sPHPT

	MEN1 all (n = 64)	*sPHPT (n = 469)*	*p (MEN1 vs. sPHPT)*	*CF*	*SI units*
Age (yr)	44.2 ± 16.1 (17–70)	60.1 ± 13.5 (10–96)	0.000		
Sex (male/female)	20/44	93/376	0.049*		
YSM† (yr)	5.1 ± 7.8 (0–28)	12.5 ± 10.8 (0–58)	0.000		
25(OH)D (ng/ml)	21.7 ± 8.8 (9.2–58.4)	22.0 ± 10.8 (4.7–97)	0.830	2.496	nM
$Ca_{alb\ adj}$ (mg/dl)	11.12 ± 0.79 (9.9–13.9)	11.18 ± 0.95 (9.5–17.2)	0.624	0.2495	mM
Ca^{2+} (mM)	1.49 ± 0.11 (1.33–1.87)	1.48 ± 0.14 (1.31–2.45)	0.584		
P (mg/dl)	2.38 ± 0.52 (1.4–3.6)	2.56 ± 0.45 (1.3–3.6)	0.003	0.3229	mM
PTH (pg/ml)	113.8 ± 69.5 (22–345)	173.7 ± 135.0 (32.8–973)	0.001	1.0	ng/L
Patients with normal PTH (%)	16 (25.0)	23 (4.9)	0.000*		
Patients <50 yr of age with normal PTH (%)	15 (37.5)	5 (5.7)	0.000*		
Creatinine (mg/dl)	0.80 ± 0.16 (0.5–1.2)	0.88 ± 0.26 (0.29–2.15)	0.055	88.40	mcM
ALP (U/liter)	127.4 ± 62.2 (36–445.5)	133.3 ± 79.9 (33–799)	0.569	0.01667	mckat/L
Creatinine clearance (ml/min)	97.0 ± 32.9 (40.0–165.0)	74.8 ± 28.1 (14.4–251.0)	0.000	0.0167	ml/s
Calcium clearance (mM GFR)	0.024 ± 0.038 (0.003–0.319)	0.024 ± 0.025 (0.001–0.300)	0.824		
24-h urinary calcium (mg/24 h)	341.5 ± 142.0 (80.0–952.9)	314.4 ± 176.8 (25–1323)	0.239	0.02495	mmol/d
Patients with renal complications (%)	37 (57.8)	259 (55.2)	0.789		
LS BMD (Z-score)	−1.33 ± 1.23 (−3.80–2.30)	−0.74 ± 1.40 (−5.00–4.65)	0.008		
FN BMD (Z-score)‡	−1.13 ± 0.96 (−3.00–1.30)	−0.60 ± 1.07 (−4.00–5.27)	0.002		

Sporadic and MEN١-Related Primary Hyperparathyroidism :Differences in Clinical Expression and Severity. Journal of Bone and Mineral Research(٢٠٠٩)

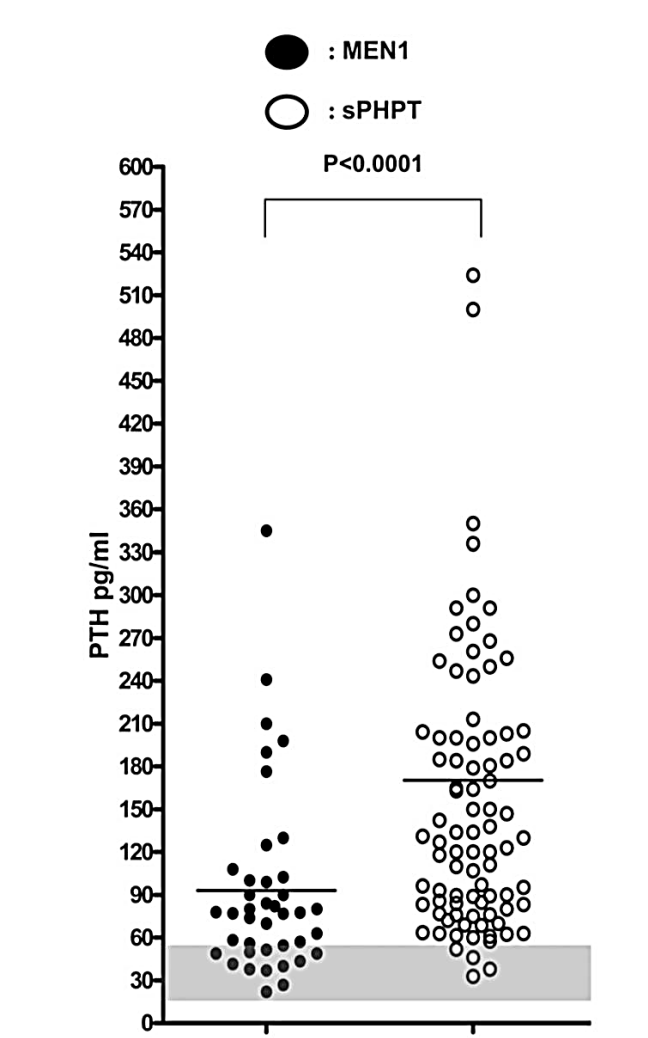

FIG. 1. PTH levels in patients <50 yr of age affected with sPHPT and MEN1-related PHPT. Gray area, PTH normal range; full circle and empty circle, MEN1 and sPHPT patients, respectively.

Sporadic and MEN1-Related Primary Hyperparathyroidism :Differences in Clinical Expression and Severity. Journal of Bone and Mineral Research(2009)

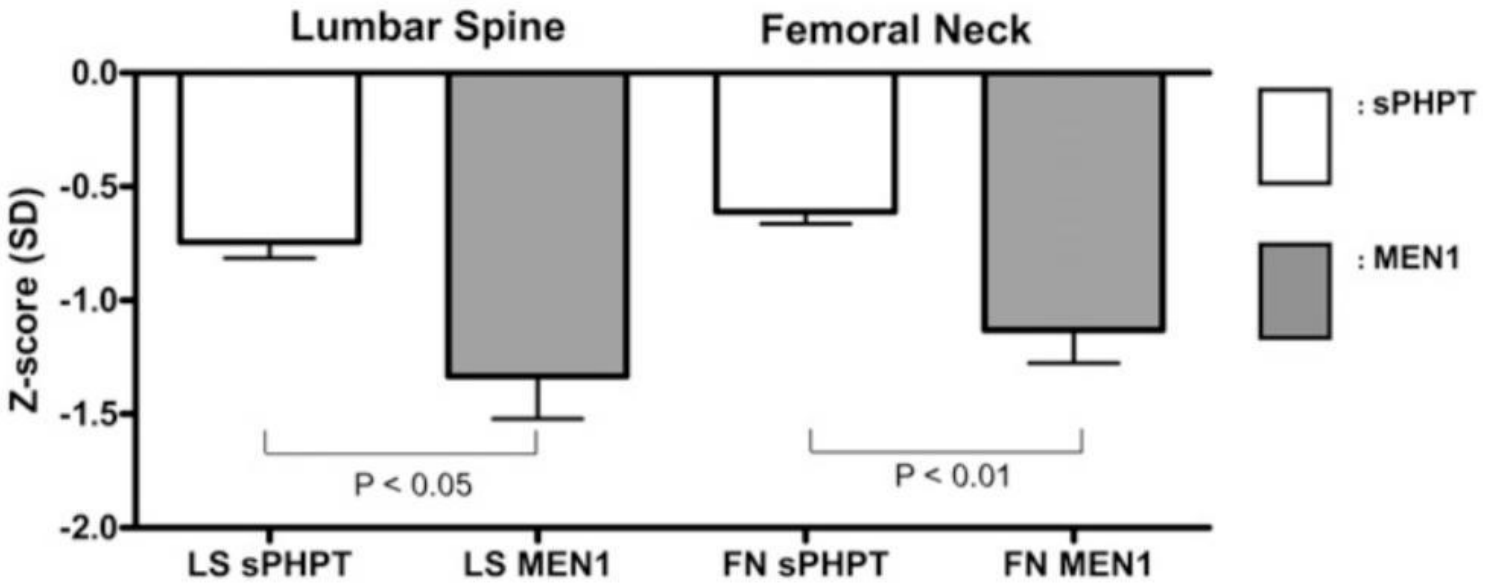

FIG. 2. BMD at the LS and FN in patients affected with sPHPT and MEN1-related PHPT. White and gray columns, sPHPT and MEN1 patients, respectively.

Sporadic and MEN1-Related Primary Hyperparathyroidism :Differences in Clinical Expression and Severity. Journal of Bone and Mineral Research(2009)

Clinical Endocrinology (2010) 72, 462–468 doi: 10.1111/j.1365-2265.2009.03672.x

ORIGINAL ARTICLE

Bone mineral density analysis in patients with primary hyperparathyroidism associated with multiple endocrine neoplasia type 1 after total parathyroidectomy

Flavia L. Coutinho*, Delmar M. Lourenço Jr*, Rodrigo A. Toledo*, Fabio L. M. Montenegro†, Joya E. M. Correia-Deur* and Sergio P. A. Toledo*

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Table 2. Biochemical and hormonal parameters performed before and 12 months after total PTx in patients with HPT associated with MEN1

	n	Before mean/(range)	After mean/(range)	*P*-value	Reference values (unit)
Intact PTH (ng/l)	16	108·7 ± 42·30 (52·6–232)	28·3 ± 11·29 (11–52)	<0·0001*	11–62 (ng/l)
Serum calcium (mmol/l)	16	2·77 ± 0·125 (2·55–2·95)	2·25 ± 0·180 (1·95–2·52)	<0·0001*	2·15–2·55 (mmol/l)
Serum phosphorus (mmol/l)	16	0·81 ± 0·136 (0·48–1·03)	1·16 ± 0·160 (0·90–1·42)	<0·0001*	0·87–1·45 (mmol/l)
Urinary calcium (mmol/24 h)	14	5·6 ± 1·69 (3·8–13·02)	3·2 ± 1·48 (2·17–5·81)	0·11	2·5–8·0 (mmol/24 h)
25-OH D (nmol/l)	11	52·42 ± 26·46 (27·46–114·82)	58·41 ± 22·19 (17·22–99·84)	0·62	22·46–93·85 (nmol/l)
Alkaline phosphatase (U/l)	15	99·2 ± 27·40 (58·0–159·3)	71·3 ± 28·33 (49·0–160·0)	0·003*	M: 40–129 (U/l) F: 35–104 (U/l)
Osteocalcin (nmol/l)	11	5·78 ± 2·92 (2·34–10·77)	2·14 ± 0·76 (0·86–3·64)	0·007*	M: 2·39–7·87 (nmol/l) F: 1·88–7·35 (nmol/l)
CTX (ng/ml)	8	0·49 ± 0·203 (0·26–1·14)	0·15 ± 0·089 (0·02–0·83)	0·014*	M: <0·70 (ng/ml)** F: <0·57 (ng/ml)

PTx, parathyroidectomy; HPT, hyperparathyroidism; MEN1, multiple endocrine neoplasia type 1; *n*, number of patients; PTH, parathyroid hormone; 25-OHD, 25 hydroxyvitamin D; CTX: C-terminal cross-linking telopeptide of type I collagen.
*$P < 0.05$; **Age 50–70 years.

Table 3. BMD analysis by DXA performed before and 15 months after PTx in 16 patients with HPT associated with MEN1

	Before mean ± SD (range)	After mean ± SD (range)	*P*-value
Lumbar spine, g/cm^2	0·843 ± 0·183 (0·576–1·247)	0·909 ± 0·183 (0·550–1·284)	0·001*
Lumbar spine, *Z*-score	−1·84 ± 1·602 (−4·13/+1·83)	−1·18 ± 1·590 (−4·27/+2·18)	0·0004*
Lumbar spine, *T*-score	−2·12 ± 1·731 (−4·69/+1·82)	−1·51 ± 1·729 (−4·92/+2·15)	0·0007*
Femoral neck, g/cm^2	0·745 ± 0·106 (0·525–0·886)	0·798 ± 0·087 (0·618–0·923)	0·0001*
Femoral neck, *Z*-score	−1·08 ± 1·117 (−3·62/+0·41)	−0·53 ± 0·994 (−2·65/+0·87)	<0·0001*
Femoral neck, *T*-score	−1·89 ± 1·029 (−3·74/−0·08)	−1·40 ± 0·811 (−2·77/−0·10)	0·0001*
Total femur, g/cm^2	0·818 ± 0·113 (0·630–1·004)	0·874 ± 0·120 (0·660–1·081)	<0·0001**
Total femur *Z*-score	−1·29 ± 0·899 (−3·13/+0·42)	−0·78 ± 1·008 (−2·61/+1·12)	<0·0001**
Total femur, *T*-score	−1·72 ± 0·914 (−3·40/+0·24)	−1·27 ± 1·006 (−2·92/+0·89)	<0·0001**
1/3 distal radius, g/cm^2	0·627 ± 0·089 (0·374–0·729)	0·622 ± 0·075 (0·434–0·708)	0·76
1/3 distal radius, *Z*-score	−2·00 ± 1·534 (−5·03/+0·04)	−2·00 ± 1·447 (−4·32/+0·25)	0·96
1/3 distal radius, *T*-score	−2·39 ± 1·627 (−5·65/−0·20)	−2·46 ± 1·547 (−5·20/−0·62)	0·53
Ultra distal radius, g/cm^2	0·518 ± 0·048 (0·425–0·296)	0·506 ± 0·056 (0·305–0·452)	0·24
Ultra distal radius, Z-score	−2·18 ± 1·379 (−3·30/+0·55)	−2·22 ± 1·288 (−2·85/−0·46)	0·84
Ultra distal radius, *T*-score	−2·53 ± 1·371 (−4·04/+0·26)	−2·64 ± 1·365 (−3·65/−0·74)	0·59

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; bone mineral density was expressed as g/cm^2; *T*-scores (difference from the mean BMD value in a healthy young reference population) and *Z*-scores (age-matched comparison) were expressed in SD units.
*$P < 0·05$.

Bone Mineral Density Analysis in Patients with Primary Hyperparathyroidism Associated with Multiple Endocrine Neoplasia Type ١ After Total Parathyroidectomy .Clinical Endocrinology(٢٠١٠)

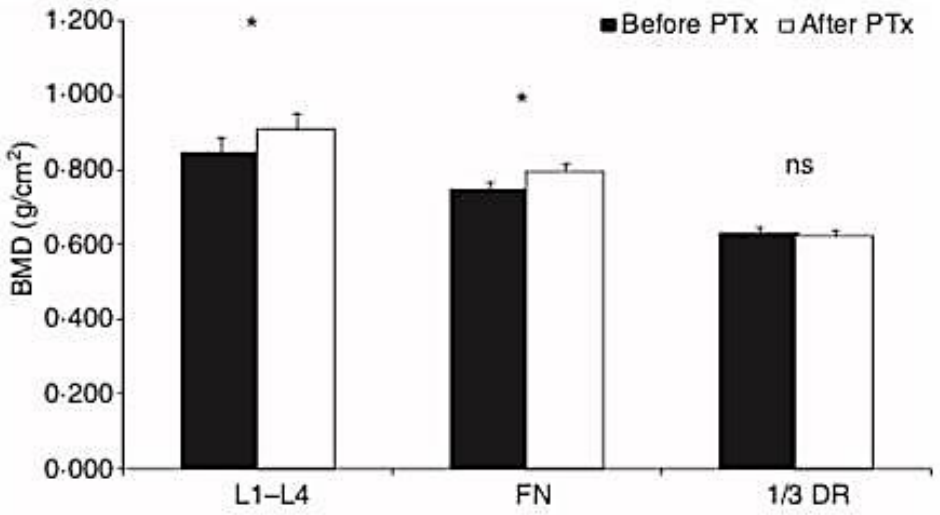

Fig. 1 Bone mineral density values (mean ± SEM) in the lumbar spine (L1–L4), femoral neck and proximal one-third of the distal radius (1/3 DR) before (black bars) and 15 months after (white bars) total parathyroidectomy, followed by parathyroid auto-implant in the forearm in 16 patients with primary hyperparathyroidism associated with multiple endocrine neoplasia type 1; * $P \leq 0.001$; ns, not statistically significant. Error bars represent standard error of the mean.

Bone Mineral Density Analysis in Patients with Primary Hyperparathyroidism Associated with Multiple Endocrine Neoplasia Type 1 After Total Parathyroidectomy .Clinical Endocrinology(2010)

Table II. HPT characteristics by patient group

	MEN1/HPT n, (%)	*sHPT* n, (%)	P *value*
Median age at operation, y (min–max)	41.5 (14.0–71.0)	61.0 (28–88)	.0016
Median time from diagnosis to operation, mo (min–max)	6.0 (0–61)	4.0 (0.5–142)	.4500
Median serum PTH preoperative, pg/mL (min–max)	120.0 (44.0–615.0)	99.0 (39–233)	.1400
Median serum PTH postoperative, pg/mL (min–max)	57 (5.0–77.0)	41 (10.0–106.0)	.7600
Median serum calcium preoperative, mg/dL (min–max)	10.8 (10.3–11.6)	10.6 (9.5–13.7)	.0654
Median serum calcium postoperative, mg/dL (min–max)	9.5 (7.9–10.4)	9.5 (8.3–10.5)	.5300
Median adjusted calcium, mg/dL (min–max)	10.5 (10.06–11.58)	10.4 (8.9–13.0)	.3600
Criteria for operation			
Serum calcium >1 mg/dL*	6 (43)	56 (54)	.6100
24-h urine for calcium >400 mg/d	1 (7)	9 (9)	
T-score <–2.5	5 (36)	29 (27)	
<50 years old	2 (14)	6 (6)	
Inability to adhere to long-term follow-up	0	4 (4)	
Normocalcemic hyperparathyroidism			
No	7 (50)	62 (60)	.5700
Yes	7 (50)	42 (40)	
Operation type			
Total ptx	—	—	<.0001
Subtotal ptx	13 (93)	4 (4)	
Less than subtotal ptx	1 (7)	100 (96)	

*>upper limit of normal.
Ptx, Parathyroidectomy.

Operative Intervention for Primary Hyperparathyroidism offers Greater Bone Recovery in Patients with Sporadic Disease than in those with Multiple Endocrine Neoplasia Type ١-related Hyperparathyroidism. Surgery(٢٠١٦)

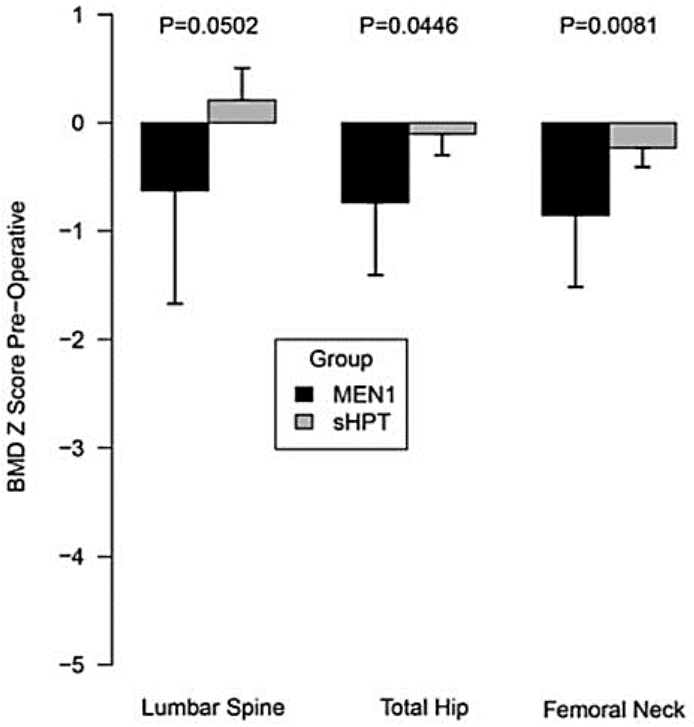

Fig 2. Preoperative Z-score by patient group.

Table IV. Comparison of patient absolute outcomes before and 1 year after operative intervention in the MEN1/HPT group and in the SHPT, respectively

		Preoperative			*Postoperative*		
	n	*Mean*	*SD*	n	*Mean*	*SD*	P *value*
MEN1/HPT							
BMD							
LS	14	0.95	0.20	14	0.97	0.17	.8600
TH	12	0.82	0.13	14	0.86	0.11	.6200
FN	13	0.75	0.10	14	0.74	0.10	.2400
Z-score							
LS	13	−0.63	1.88	14	−0.49	1.74	.0200
TH	12	−0.74	1.15	14	−0.75	1.11	.5000
FN	12	−0.86	1.14	14	−0.78	1.12	.6300
sHPT							
BMD							
LS	104	0.95	0.16	92	0.98	0.17	.0001
TH	104	0.83	0.16	*92*	0.85	0.17	.1300
FN	104	0.70	0.15	92	0.72	0.14	.0585
Z-score							
LS	100	0.21	1.48	91	0.54	1.50	<.0001
TH	104	−0.11	1.01	92	0.05	1.06	.0004
FN	104	−0.24	0.90	92	−0.08	0.92	.0001

P value results from paired t test.

Operative Intervention for Primary Hyperparathyroidism offers Greater Bone Recovery in Patients with Sporadic Disease than in those with Multiple Endocrine Neoplasia Type 1-related Hyperparathyroidism. Surgery (2016)

Treatment of PHPT in MEN١

- Surgery is treatment of choice ,indications are similar to sporadic form(ZES)
- Optimal time ,type & extent are unclear
- Some experts favor early intervention to reduce risk of bone disease
- Some prefer delaying surgery for limiting the number of surgeries.
- Subtotal parathyroidectomy(٣,٥/٤)
- Transcervical thymectomy is recommended in all MEN١ patient
- Cinacalcet: surgery failure/poor surgical candidate(decrease ca,no effect on BMD or hypercalciuria)

frontiers in Endocrinology

ORIGINAL RESEARCH
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When Parathyroidectomy Should Be Indicated or Postponed in Adolescents With MEN1-Related Primary Hyperparathyroidism

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Department of Surgery and Translational Medicine, University of Florence, Florence, Italy

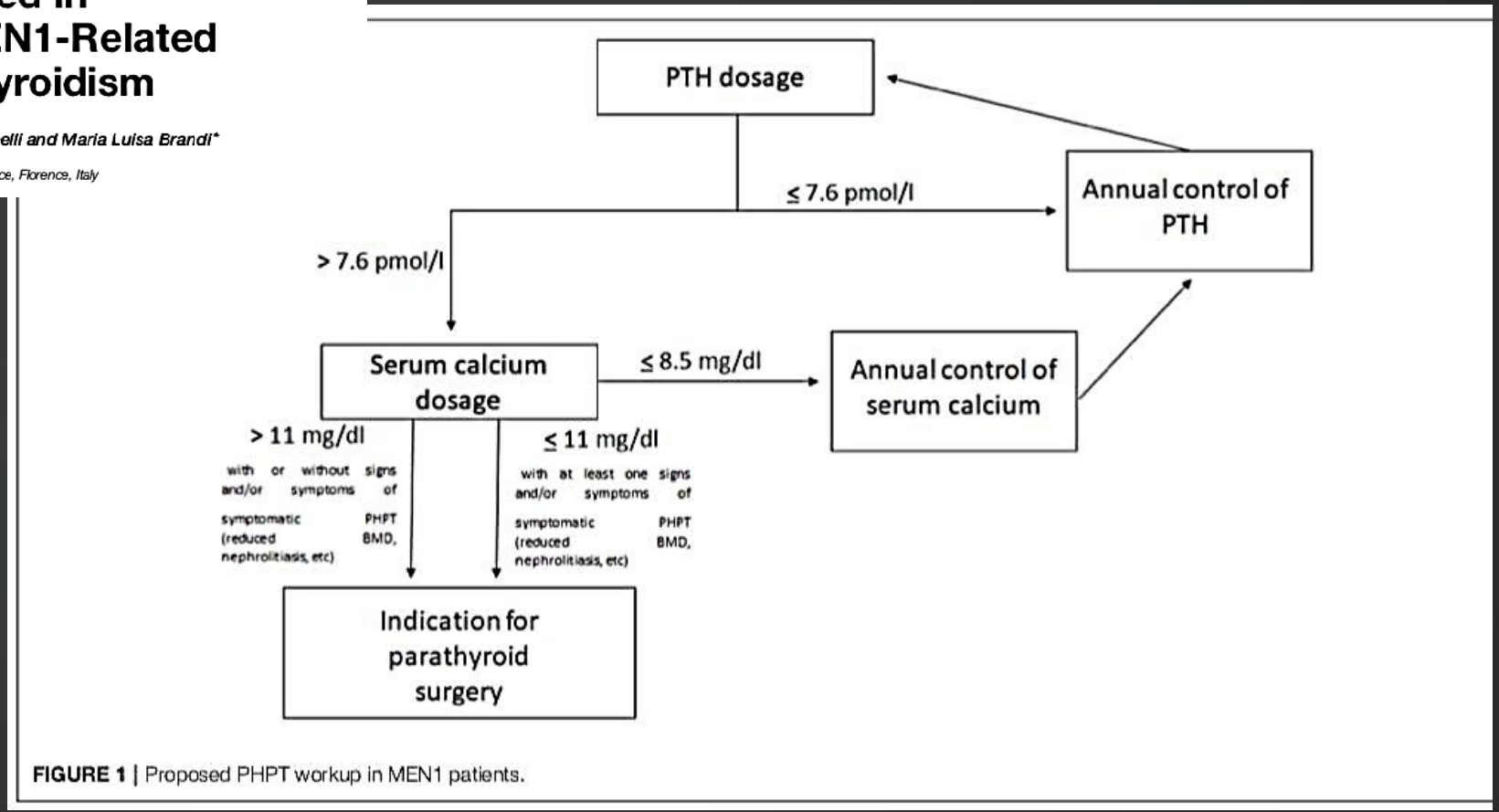


FIGURE 1 | Proposed PHPT workup in MEN1 patients.

World J Surg (2011) 35:1993–2005
DOI 10.1007/s00268-011-1068-9

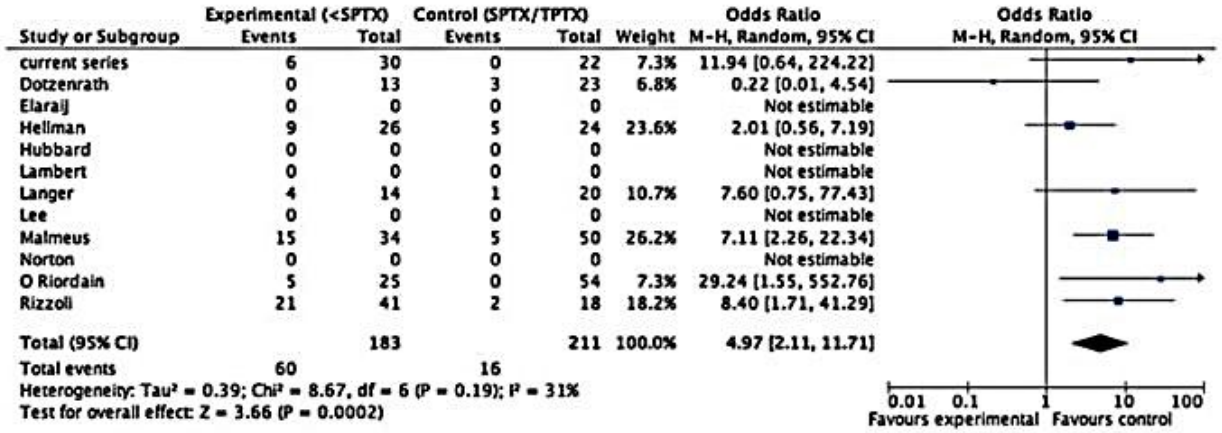
World Journal of Surgery

The Optimal Surgical Treatment for Primary Hyperparathyroidism in MEN1 Patients: A Systematic Review

Jennifer M. J. Schreinemakers · Carolina R. C. Pieterman · Anouk Scholten · Menno R. Vriens · Ge
Inne H. M. Borel Rinkes

Published online: 29 June 2011

Appendix C1: Comparison of <SPTX versus SPTX/TPTX on persistent pHPT



Study or Subgroup	Experimental (<SPTX) Events	Total	Control (SPTX/TPTX) Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
current series	6	30	0	22	7.3%	11.94 [0.64, 224.22]
Dotzenrath	0	13	3	23	6.8%	0.22 [0.01, 4.54]
Elaraij	0	0	0	0		Not estimable
Hellman	9	26	5	24	23.6%	2.01 [0.56, 7.19]
Hubbard	0	0	0	0		Not estimable
Lambert	0	0	0	0		Not estimable
Langer	4	14	1	20	10.7%	7.60 [0.75, 77.43]
Lee	0	0	0	0		Not estimable
Malmeus	15	34	5	50	26.2%	7.11 [2.26, 22.34]
Norton	0	0	0	0		Not estimable
O Riordain	5	25	0	54	7.3%	29.24 [1.55, 552.76]
Rizzoli	21	41	2	18	18.2%	8.40 [1.71, 41.29]
Total (95% CI)		183		211	100.0%	4.97 [2.11, 11.71]
Total events	60		16			

Heterogeneity: Tau² = 0.39; Chi² = 8.67, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 3.66 (P = 0.0002)

<SPTX fewer than 3 parathyroid glands resected, *SPTX* 3–3½ parathyroid glands resected, *TPTX* total parathyroidectomy with autotransplantation, SPTX and TPTX are analyzed together

After <SPTX, patients are more likely to develop persistent pHPT than after SPTX/TPTX (OR = 4.97, 95% CI = 2.11–11.71, $P = 0.0002$)

World J Surg (2011) 35:1993–2005
DOI 10.1007/s00268-011-1068-9

World Journal of Surgery

The Optimal Surgical Treatment for Primary Hyperparathyroidism in MEN1 Patients: A Systematic Review

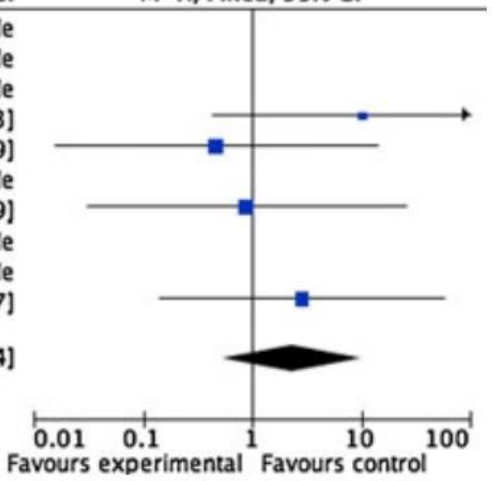
Jennifer M. J. Schreinemakers · Carolina R. C. Pieterman · Anouk Scholten · Menno R. Vriens · Gerlof D. Valk · Inne H. M. Borel Rinkes

Published online: 29 June 2011

Appendix C2: Comparison of SPTX versus TPTX for persistent pHPT

Study or Subgroup	Experimental (SPTX) Events	Total	Control (TPTX) Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
current series	0	16	0	6		Not estimable
Dotzenrath	0	25	0	1		Not estimable
Elaraij	0	21	0	4		Not estimable
Hellman	2	9	0	15	11.3%	10.33 [0.44, 243.33]
Hubbard	3	25	0	1	31.6%	0.47 [0.02, 13.89]
Lambert	0	0	0	0		Not estimable
Langer	0	5	1	15	29.5%	0.88 [0.03, 24.99]
Lee	0	0	0	0		Not estimable
Malmeus	0	4	0	18		Not estimable
Norton	5	41	0	9	27.6%	2.86 [0.15, 56.47]
Total (95% CI)		**146**		**69**	**100.0%**	**2.37 [0.54, 10.44]**
Total events	10		1			

Heterogeneity: $Chi^2 = 2.07$, $df = 3$ ($P = 0.56$); $I^2 = 0\%$
Test for overall effect: $Z = 1.14$ ($P = 0.25$)



questions

- what are the prevalence of MEN ١ components?
- What are the factors influencing the prevalence?
- Is there a genotype phenotype correlation?
- What are the difference between neuroendocrine tumor in MEN ١ & sporadic tumors?
- What is the relationship between prolactinoma & weight gain in our patient?

Reviews in Endocrine and Metabolic Disorders (2019) 20:197–206
https://doi.org/10.1007/s11154-019-09503-1

Prolactin and human weight disturbances: A puzzling and neglected association

Luis G. Sobrinho[1] · Nelson D. Horseman[2]

Published online: 6 May

Table 1 Frequency of Overweight in Patients with Prolactinomas

Author (Ref)	Nr Sex	% overweight	Definition of overweight	Macro/Micro-prolactinoma
Forbes et al. [1]	15 F	9/15. Range 22 to over 60 pounds overweight.	Pounds overweight compared to the norm.	Pre CT scan
Nunes et al. [3]	35 F	Average excess weight 35% v. 11% in controls ($p < 0.01$)	% of excess weight above the norm.	Pre CT scan
Creemers et al. [6]	18 F; 29 M	Nr with BMI=> 25 Kg/m^2: M ($p < 0.001$); F (n.s.).	BMI compared to the average Dutch population	Micro =11 Macro = 36
Wallace et al. [9]	157 F	Ten pounds heavier than controls ($p < 0.05$). Height was similar in both groups.	Pounds overweight compared to age-matched controls	Pre CT scan
Schmid et al. [10]	126 F; 55 M	Macro −25% v. 4,5% Micro – 9.9% v. 4%	BMI = > 30 Kg/m^2 v. controls	Macro = 100 Micro = 81
Cohen et al. [11]	16 M	11/16	"Adiposity" undefined	Pre CT scan

Legend to Table 1 – Nr – Number of subjects; F - Females; M – Males; n.s. - Difference not significant; Pre CT scan – Series reported before CT scan was widely available

European Journal of Endocrinology (2003) **148** 325–331 ISSN 0804-4643

CLINICAL STUDY

Gender differences in the prevalence, clinical features and response to cabergoline in hyperprolactinemia

Annamaria Colao, Antonella Di Sarno, Paolo Cappabianca[1], Franc
Carolina Di Somma, Antongiulio Faggiano, Bernadette Biondi and

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[2]Section of Neuroradiology, 'Federico II' University of Naples, via S. Pansini 5, 80131 N

۲۱۳ patient
Weight gain (۸-۲۲ kg)

Table 1 Patients' profile at study entry. Data are shown as means±S.D. Presenting symptoms are expressed as number of individual patients with prevalence in parentheses.

	Women	Men	*P*
Total number	145	74	<0.0001
Median age (years (mean±S.D.))	29 (32.2±11.5)	32 (35.0±13.5)	0.1
Macroprolactinoma	49	58	0.2
Age median (years)	33 (36±14)	33 (36±14)	0.9
Basal prolactin levels (μg/l)	1132±2351	2848±2954	0.001
Maximal tumor diameter (mm)	17.2±7.2	25.8±12.4	<0.0001
Patients with pituitary hormone deficiency (*n*)	25 (51%)	34 (59%)	0.4
Patients with visual field defects (*n*)	18 (37%)	28 (48%)	0.6
Headache (*n*)	34 (69%)	22 (38%)	0.02
Galactorrhea (*n*)*	37 (75%)	13 (22%)	<0.0001
Infertility (*n*)**	12 (24%)	11 (19%)	0.8
Menstrual disturbances (*n*)***	38 (100%)	/	/
Libido disturbances (*n*)	/	48 (83%)	/
Weight gain (*n*)	46 (94%)	31 (53%)	<0.0001
Microprolactinoma	81	16	0.001
Age median (years)	28 (30±10)	28.5 (31±11)	0.7
Basal prolactin levels (μg/l)	135.4±60.5	187.8±51.8	0.002
Maximal tumor diameter (mm)	7.1±1.6	8.0±1.4	0.04
Headache (*n*)	25 (31%)	1 (6%)	0.08
Galactorrhea (*n*)	35 (43%)	0 (0%)	0.003
Infertility (*n*)**	43 (54%)	3 (19%)	0.02
Menstrual disturbances (*n*)****	62 (76%)	/	/
Libido disturbances (*n*)	/	14 (88%)	/
Weight gain (*n*)	48 (59%)	3 (19%)	0.03
Non tumoral hyperprolactinemia	15	0	0.0001
Age median (years)	28 (31±8)	/	n.a.
Basal prolactin levels (μg/l)	72±9	/	n.a.
Headache (*n*)	0 (0%)	/	n.a.
Galactorrhea (*n*)	3 (20%)	/	n.a.
Infertility (*n*)	5 (33%)	/	n.a.
Menstrual disturbances (*n*)	12 (80%)	/	n.a.
Weight gain (*n*)	8 (53%)	/	n.a.

*Either spontaneous or expressible; **as presenting complaint; ***11 women were excluded since they were ≥50 years of age; ****4 women were excluded since they were ≥50 years of age. n.a., not applicable.

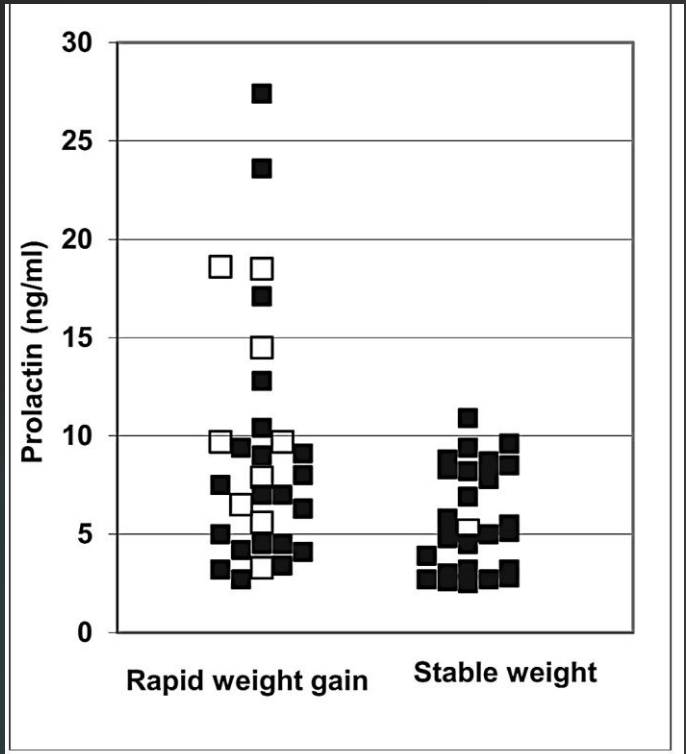


Fig. 1 Morning prolactin levels in 30 women with rapid weight gain (Group 1) and 26 controls with stable weight (Group 2). Galactorrhea was found in women represented by white squares (from [44], used with permission)

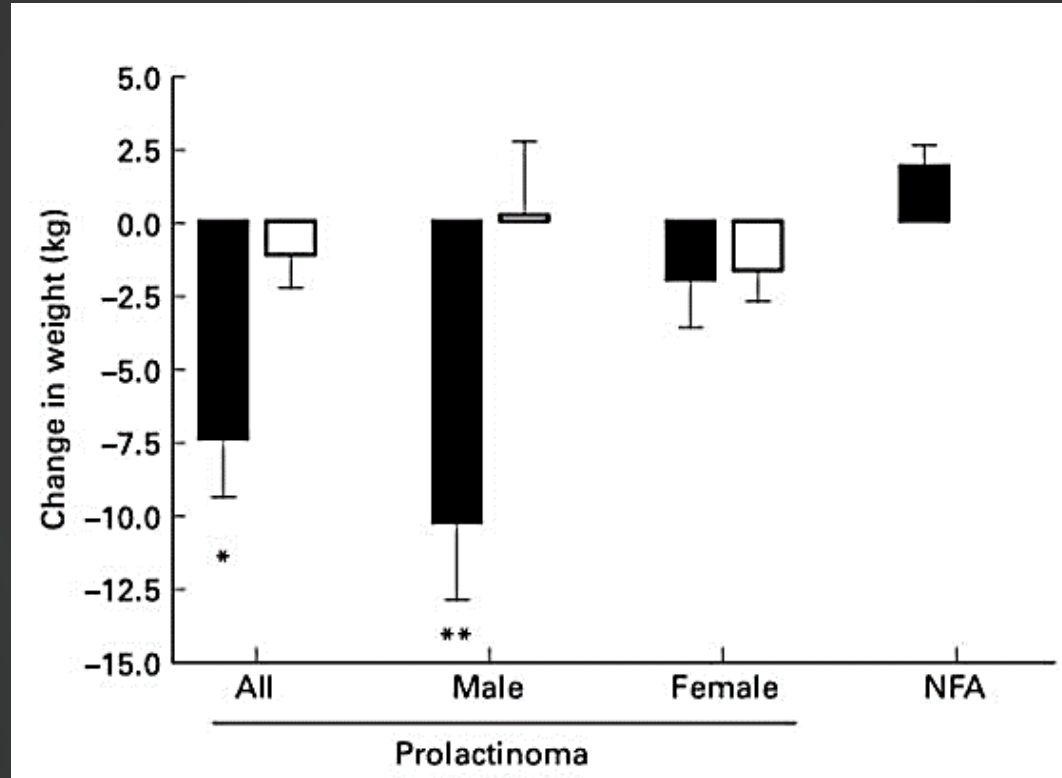


Fig. 1 Weight loss during treatment in relation to prolactin levels. Patients with prolactinoma (PR) who normalized prolactin levels during treatment (■) lost significantly more weight than those who remained hyperprolactinaemic (□). Patients suffering from non-functioning adenomas (NFA) had no significant weight changes following surgery. * $P = 0{\cdot}0081$; ** $P = 0{\cdot}0097$.

Increased Body Weight Associated with Prolactin Secreting Pituitary Adenoma. Clinical Endocrinology(۱۹۹۸)۴۸،۵۴۷-۵۵۳

Prolactinoma & weight gain

- Prolactinoma can occasionally impact on nearby neural structure, but this effect have no relationship with weight gain.
- Prolactin as an anabolic hormone: The very close relationships between prolactin and growth hormone in terms of evolution, structure, and signal transduction suggests that these hormones might share some physiological effects on metabolism.
- Adipose tissue appears to be one example of an extra pituitary source of prolactin. Although levels of prolactin secretion are minuscule compared with the pituitary, the larger number of cells might make the adipose a meaningful source of hormone .
- Prolactin induced serotonin ,beta cell proliferation .
- Weight gain in prolactinoma is inconsistent, there is no correlation between serum prolactin level &weight gain/BMI.


THANK
YOU

MEN١

- Diagnostic criteria:
  - Patient with ٢ of ٣ typical tumors of MEN ١ Syndrome
  - Patient with ١ typical MEN١ tumor + first degree relative with confirmed MEN١ mutation
  - People with confirmed MEN١ mutation without clinical/ biochemical symptoms
- Prevalence of MEN١ is estimated to be:٠/٢٥ %,average: ١:٣٠،٠٠٠
- Autosomal dominant disorder, sporadic form in ٨-١٤% patients(denovo mutation)

Pituitary tumors in MEN1 syndrome- the new insight into the diagnosis and treatment.Endrkrynologia polska 2019;70(5)

MEN ١

- The disease occurs in all age groups(٥-٨١ y/o)
- Clinical & biochemical manifestation occurs in ٨٠-١٠٠% of patients
- In over ٩٨% of cases symptoms will occur up to age of ٥٠ y/o

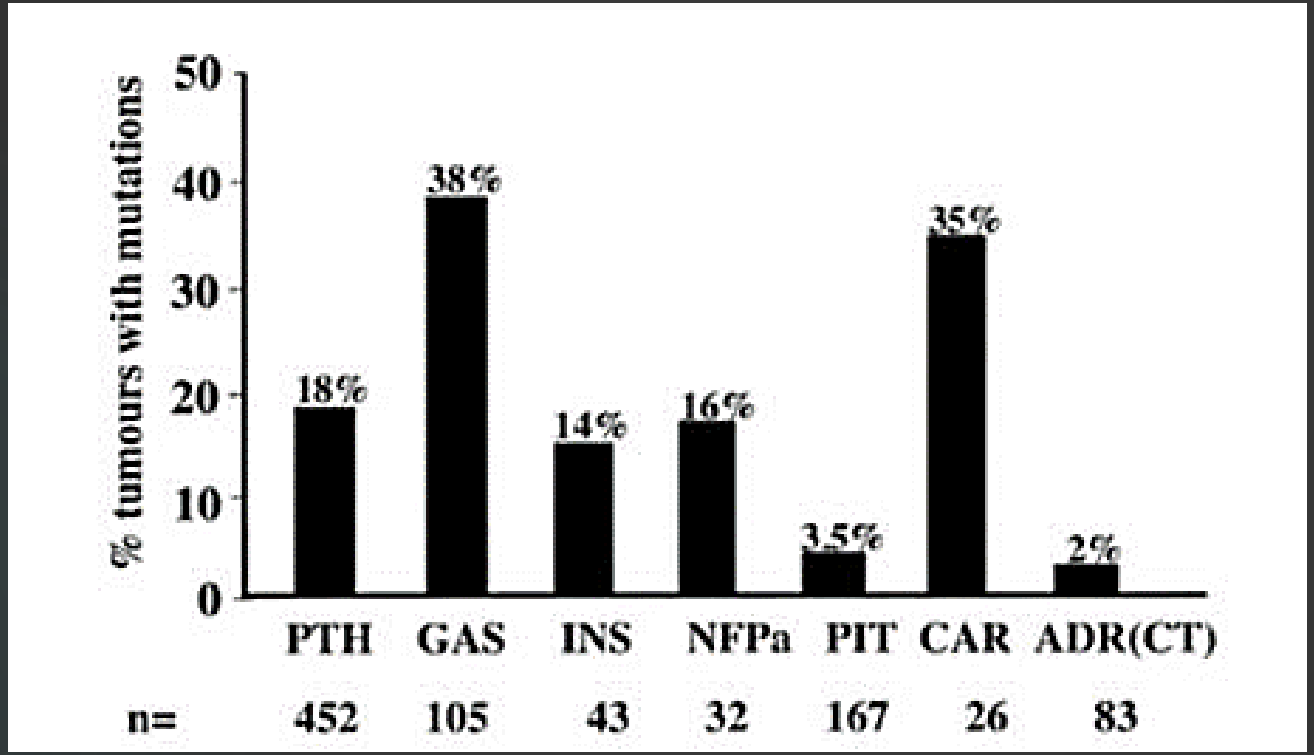
Pituitary tumors in MEN1 syndrome- the new insight into the diagnosis and treatment.Endrkrynologia polska 2019;70(5)

Detection of MEN١-RELATED TUMOR

- Pos FH of neuroendocrine tumor of pancreas,pituitary,parathyroid gland & familial occurrence of endocrine system disorders.
- Patient with Zollinger-Ellison syndrome
- Young patient with hormonally active pituitary tumors
- Multiple pancreatic tumors
- Hyperparathyroidism in patient up to ۴۵ y/o
- Multiple parathyroid adenoma
- Pituitary tumor & hypercalcemia/ other endocrinopathy

Pituitary tumors in MEN1 syndrome- the new insight into the diagnosis and treatment.Endrkrynologia polska 2019;70(5)

Frequencies of MEN١ somatic mutation in non familial tumor



Multiple endocrine neoplasia type ١,Best Practice & Research Clinical Endocrinology & Metabolism ٢٤(٢٠١٠)٣٥٥-٣٧٠