IN THE NAME OF GOD

Consensus Statement on Vitamin D Status Assessment and Supplementation: Whys, Whens, and Hows

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Review

Consensus Statement on Vitamin D Status Assessment and Supplementation: Whys, Whens, and Hows

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agenda

- **Abstract**
- **Vitamin D Metabolism and Mechanism of Action**
- **Assessment of Vitamin D Status**
- **Clinical Outcomes of Vitamin D Deficiency**
- **Vitamin D Supplementation and regimes**
- **Different Forms of Vitamin D Supplementation**
- **Vitamin D toxicity**
- **Monitoring vitamin D status during treatment**
- **Conclusions**

Abstract

- The 6th International Conference, “Controversies in Vitamin D,” was convened to discuss controversial topics, such as vitamin D metabolism, assessment, actions, and supplementation
- Optimal 25-hydroxyvitamin D (25(OH)D) levels remain debated
- The lack of assay standardization also poses challenges in interpreting data from available studies
- Beyond the well-known skeletal features, interest in vitamin D’s extra skeletal effects has led to
  clinical trials on cancer, cardiovascular risk, respiratory effects, autoimmune diseases, diabetes, and mortality
- The initial negative results are due to enrollment of vitamin D-replete individuals
- Subsequent post hoc analyses have suggested potential benefits in reducing cancer incidence, autoimmune diseases, cardiovascular events, and diabetes
- Cholecalciferol is favored due to safety and minimal monitoring requirements
- Further studies are needed to investigate vitamin D effects in relation to the different recommended 25(OH)D levels and the efficacy of the different supplementary formulations in achieving biochemical and clinical outcomes within the multifaced skeletal and extra skeletal potential effects of vitamin D.

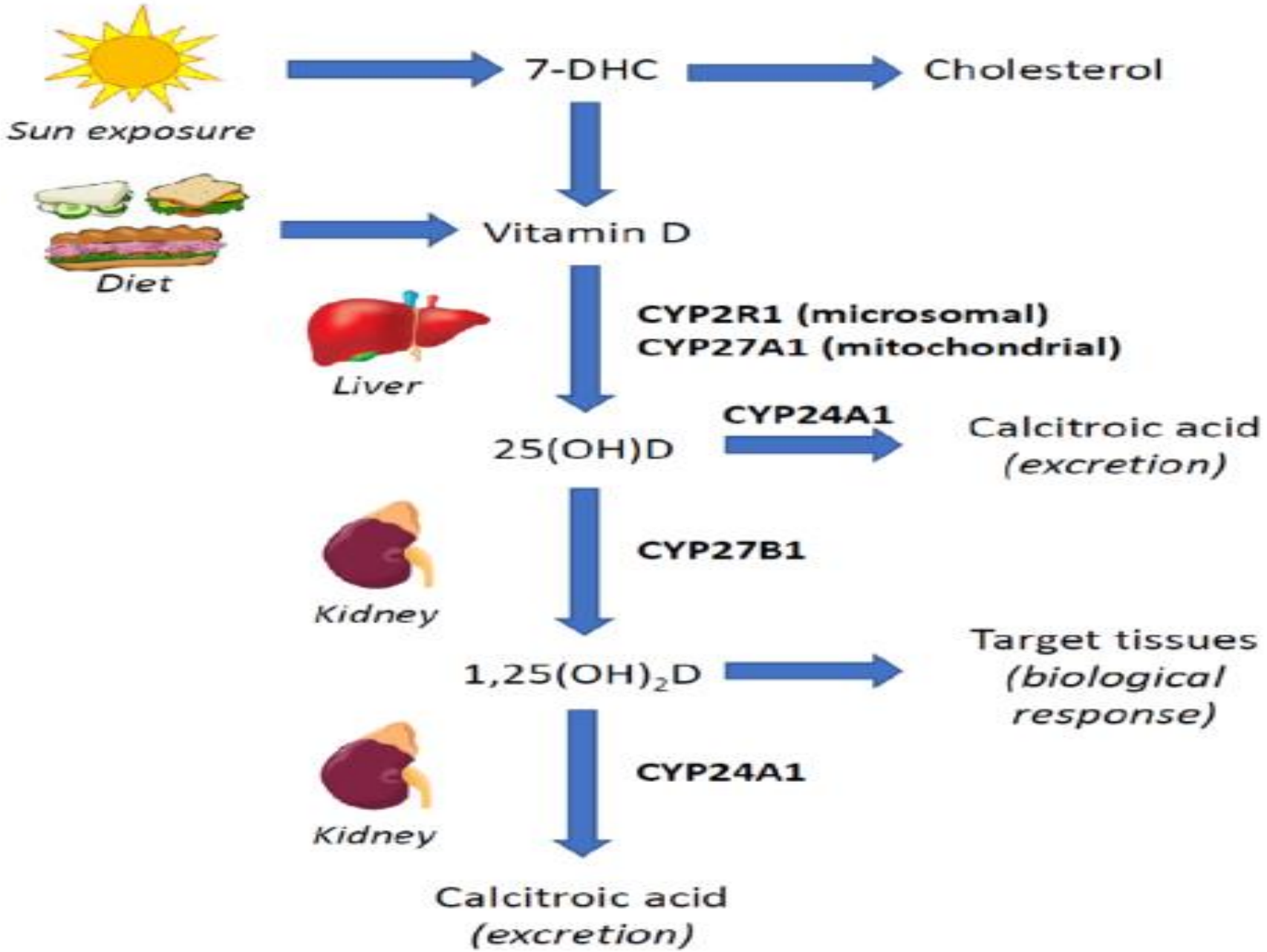
Vitamin D Metabolism and Mechanism of Action

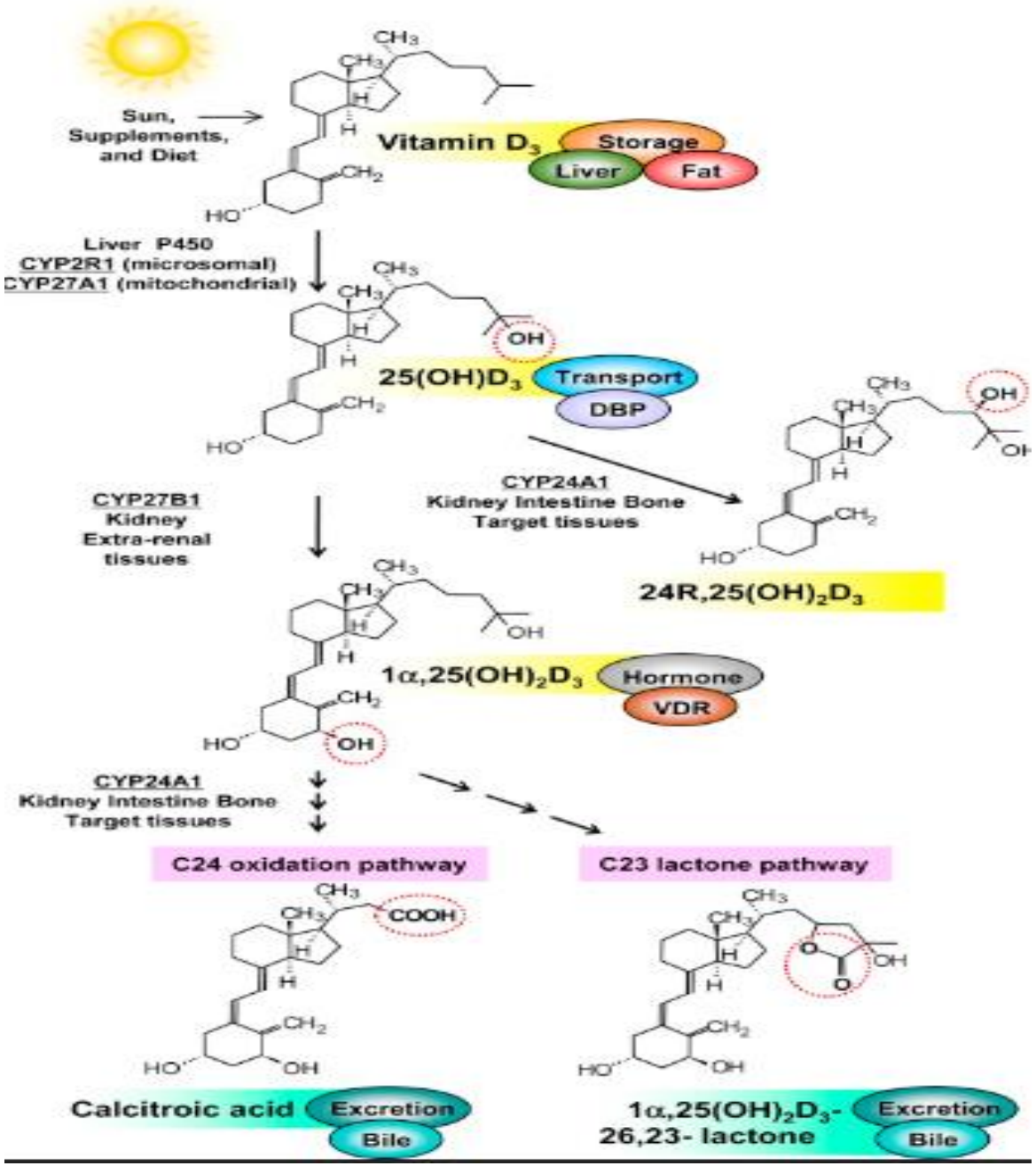
- Metabolism
- 7-Dehydrocholesterol reductase
- 25-Hydroxylases
- CYP27B1—the 25-hydroxyvitamin D–1α-hydroxylase
- CYP24A1 and CYP3A—the 25-hydroxyvitamin D–24(23) hydroxylases
- Mechanism of Action
- Regulation
- Genomic actions
- Coregulators and epigenetic changes regulating vitamin D receptor function

Metabolism

- Vitamin D3 is produced in the skin from 7-dehydrocholesterol (7-DHC)
- while both vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) can be present in the diet
- Vitamin D2 and D3 are hydroxylated first in the liver (and other tissues) to 25-hydroxyvitamin D (25(OH)D)
- then in the kidney (and other tissues) to 1,25 dihydroxy vitamin D (1,25(OH)2D)
- Both 25(OH)D and 1,25(OH)2D are subsequently metabolized to their 24 (and for D3 23) hydroxy forms 24,25(OH)2D2/3, 23,25(OH)2D3, and 1,24,25(OH)3D2/3 (or 1,23,25(OH)3D3)
- highly lipophilic
- The half-life :

  25(OH)D is 2 to 3 weeks
  1,25(OH)2D is approximately 5 to 8 hours
- The majority of circulating 25(OH)D, including its metabolites, are bound tightly by vitamin D binding protein (DBP) and more loosely bound by albumin


Sun exposure
7-DHC
Cholesterol
Diet
Vitamin D
Liver
CYP2R1 (microsomal)
CYP27A1 (mitochondrial)
25(OH)D
CYP24A1
Calcitroic acid
(excretion)
Kidney
CYP27B1
1,25(OH)2D
Target tissues
(biological
response)
Kidney
CYP24A1
Calcitroic acid
(excretion)


Sun,
Supplements,
and Diet
Vitamin D3
Storage
Liver
Fat
Liver P450
CYP2R1 (microsomal)
CYP27A1 (mitochondrial)
25(OH)D3
Transport
DBP
CYP24A1
Kidney Intestine Bone
Target tissues
24R,25(OH)2D3
CYP27B1
Kidney
Extra-renal
tissues
1α,25(OH)2D3
Hormone
VDR
CYP24A1
Kidney Intestine Bone
Target tissues
C24 oxidation pathway
C23 lactone pathway
Calcitroic acid
Excretion
Bile
1α,25(OH)2D3-
26,23- lactone
Excretion
Bile

7-Dehydrocholesterol reductase

- Although the production of vitamin D from 7-DHC under the influence of sunlight (UVB) is a nonenzymatic step, the production of 7-DHC is not
- Its synthesis in the skin is a step in the Kandutsch-Russell pathway
- DHCR7 converts 7-DHC to cholesterol, so its activity dictates how much 7-DHC is available for vitamin D production
- Inactivating mutations of DHCR7 result in Smith-Lemli-Opitz syndrome, a developmental disorder

- Cholesterol and vitamin D (but not 1,25(OH)2D) increase proteasomal degradation of DHCR7, leading to increased vitamin D production
- AMPK (adenosine monophosphate–activated protein kinase C) and protein kinase A are
potent inhibitors of DHCR7

25-Hydroxylases

- The liver is the major source of 25(OH)D production
- Initial studies suggested that CYP27A1, a mitochondrial enzyme was the major 25-hydroxylase
- Current data support CYP2R1 as the major 25-hydroxylase, at least in the liver (and testes), where it resides in the microsomal compartment
- When deleted in mice, serum 25(OH)D levels fall by over 50%, but not more
- Such data suggest that, as in the mouse, CYP2R1 could not be the only enzyme with 25-hydroxylase activity

25-Hydroxylases

- Akatsuki et al (16) found that a high-fat diet that induced obesity and type 2 diabetes (T2D), both decreased the hepatic messenger RNA and protein concentration of
  CYP2R1
- Thus, the concept that the low levels of 25(OH)D in obesity and the limited response to vitamin D supplementation in these individuals are somehow related to increased
  storage of vitamin D in fat is still controversial and needs
  further investigation

CYP27B1—the 25-hydroxyvitamin D–1α-hydroxylase

- Unlike the 25-hydroxylases, there is only a single 25(OH) D-1α-hydroxylase, CYP27B1
- Mitochondrial
- The kidney is the main source
- but many tissues, including the epidermis and other epithelial tissues, bone, placenta, and immune system cells, also express CYP27B1
- The product, 1,25(OH)2D, likely has paracrine or autocrine actions
- In the kidney, CYP27B1 is regulated primarily by parathyroid hormone **(PTH)** and **insulin-like growth factor-1**, which stimulate it
- as well as by fibroblast growth factor 23 **(FGF23) and 1,25(OH)2D** itself, which inhibit it

CYP27B1—the 25-hydroxyvitamin D–1α-hydroxylase

- Thus, the induction of CYP27B1 in these extrarenal tissues is by cytokines, and the failure of CYP27B1 in these tissues to respond to the increased circulating levels of 1,25(OH)2D and calcium account for the hypercalcemia often found in granulomatous diseases, such as sarcoidosis and lymphomas

- both the renal and extrarenal CYP27B1 have the same sequence, but their differences in regulation occur because of differences in tissue-specific multicomponent control modules within the regulatory regions of the gene.

CYP24A1 and CYP3A—the 25-hydroxyvitamin D–24(23) hydroxylases

- These are the catabolic enzymes of vitamin D metabolism
- both 25(OH)D and 1,25(OH)2D are their substrates
- CYP24A1 is the dominant 24-hydroxylase in most tissues
- CYP3A4 likely plays a role in the liver and intestine where it is highly expressed
- Both enzymes have 24-hydroxylase and 23-hydroxylase activity
- Both enzymes are induced by 1,25(OH)2D—and CYP24A1 is induced by **25(OH)D** as well
- P24A1 is under the control of **1,25(OH)2D** and **FGF23** (both stimulatory) and **calcium**

CYP24A1 and CYP3A—the 25-hydroxyvitamin D–24(23) hydroxylases

- mutations in CYP24A1 are now recognized as a major cause of idiopathic infantile hypercalcemia
- a syndrome marked by severe hypercalcemia, hypercalciuria, and nephrocalcinosis, decreased PTH, low 24,25(OH)2D, and inappropriately normal to high 1,25(OH)2D
- Although initially identified in children more recent case reports indicate that the diagnosis may not be made until adulthood, generally following a condition of increased 1,25(OH)2D production like pregnancy
- Such adults generally present with early-onset nephrolithiasis and/or nephrocalcinosis.

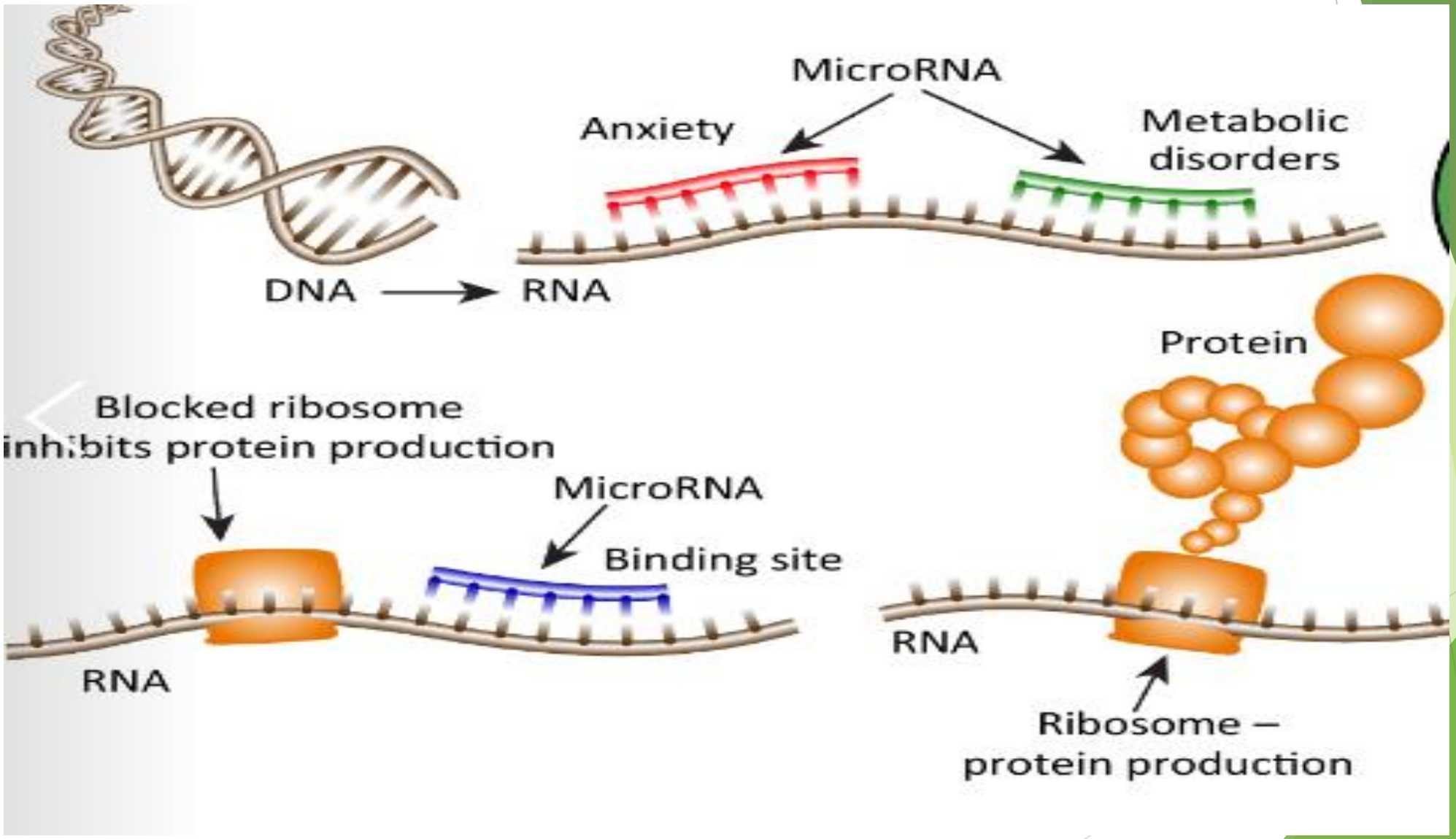
CYP24A1 and CYP3A—the 25-hydroxyvitamin D–24(23) hydroxylases

- CYP3A4 mutations or drug-induced excess CYP3A4 activity have recently been linked to vitamin D deficiency and vitamin D–dependent rickets type 3, with affected
  individuals demonstrating greatly accelerated inactivation of
  vitamin D metabolites
- This represents a novel mechanism for vitamin D deficiency

Mechanism of Action

- The VDR is critical for most of the actions of vitamin D, with 1,25(OH)2D as its major ligand. VDR is a transcription factor found in nearly all cells.
- In a recent ontology analysis 11 031 putative VDR target genes were identified
- of which 43% were involved with metabolism, 19% with cell and tissue morphology, 10% with cell junction and adhesion, 10% with differentiation and development, 9% with angiogenesis, and 5% with epithelial to mesenchymal transition
- VDR can regulate various **microRNAs (miRNAs)** and long noncoding RNAs involving the expression of numerous proteins directly or indirectly
- Although most of the actions of VDR involve its role as a transcription factor within the nucleus, the VDR has also been shown to have nongenomic actions via its location in the plasma membrane and perhaps even in mitochondria

MicroRNA

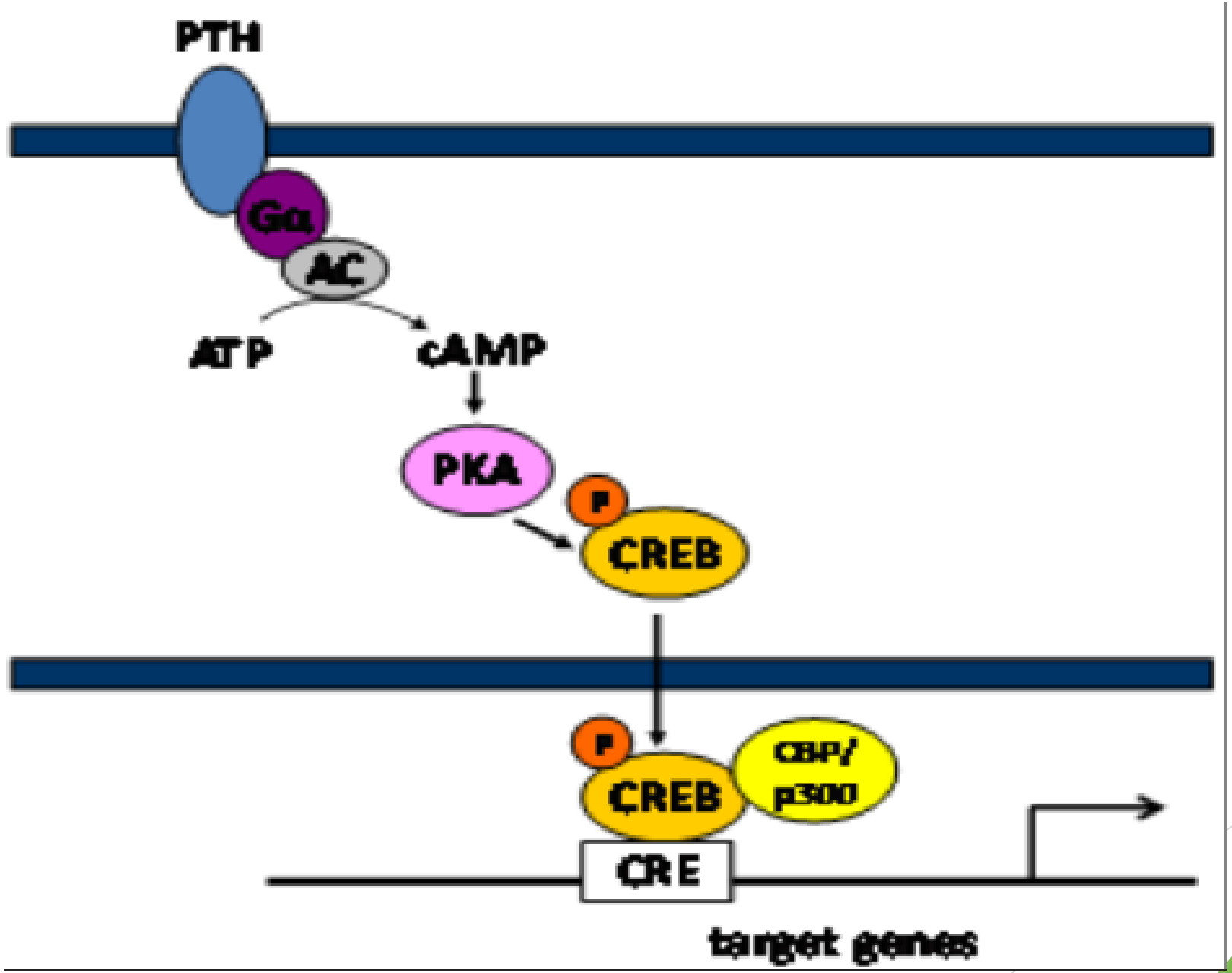

MicroRNA
Anxiety
Metabolic disorders
DNA
RNA
Protein
Blocked ribosome inhibits protein production
MicroRNA
Binding site
RNA
RNA
Ribosome – protein production

Regulation

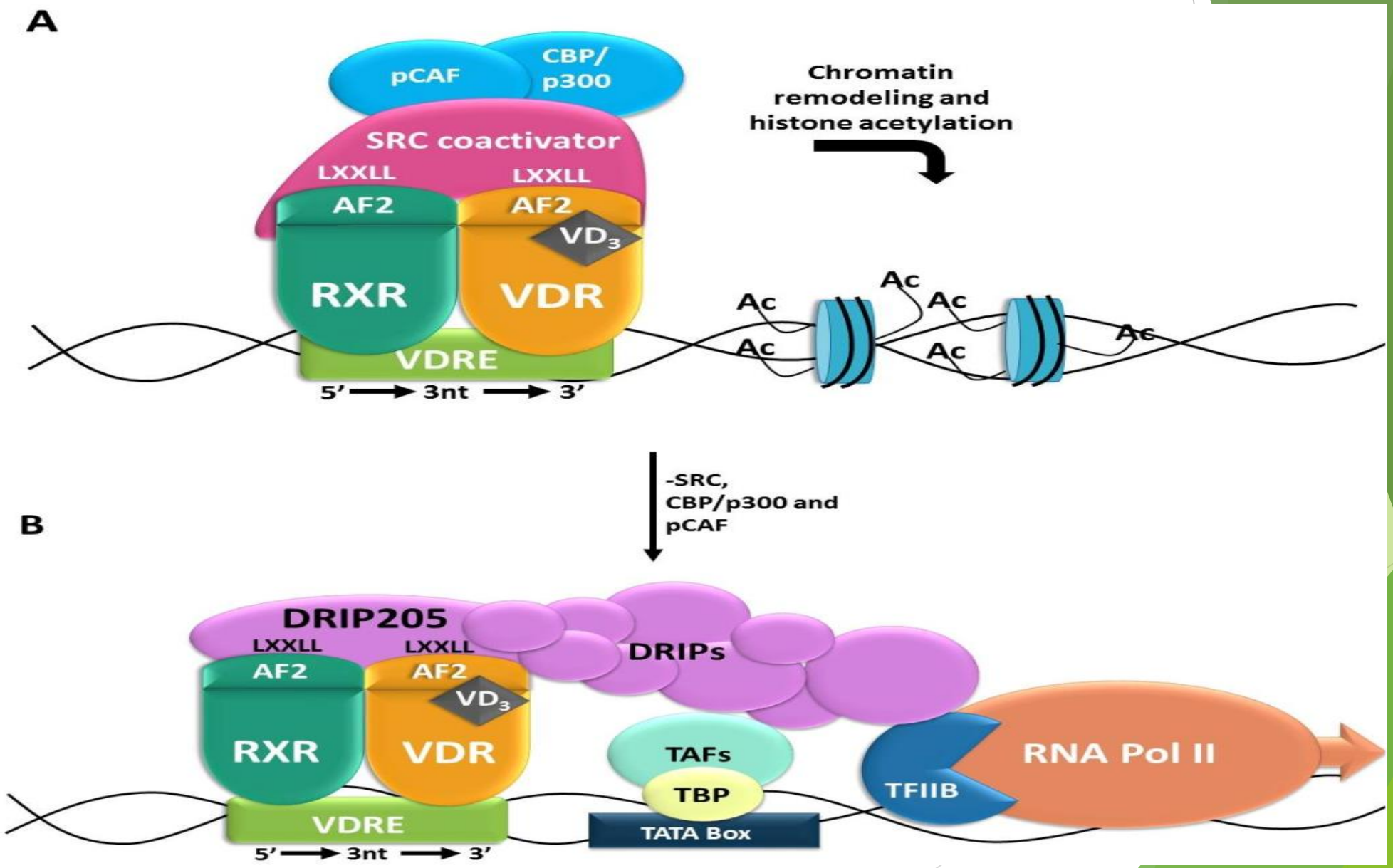
- The regulation of VDR expression is cell specific
- For example, 1,25(OH)2D regulates VDR expression in bone cells but not in the intestine
- calcium upregulates VDR expression in the parathyroid gland
- growth factors
- insulin
- PTH
- glucocorticoids
- estrogen
- retinoic acid
- in some cases acting via a variety of transcription factors

Genomic action

- human genome contains more than 23 000 VDR binding sites, most of which are cell specific
- The VDR binding sites can be thousands of bases away from the transcription start site (TSS) of the genes they regulate
- multiple VDR binding sites
- RANKL gene (*Tnfsf11*): regulated by PTH and 1,25(OH)2D in osteoblasts
- The VDR binding sites are generally situated in a region with other transcription factors that may share regulation of that gene
- VDR binding region of the *RANKL* gene contains several CREB sites responsible for the PTH regulation of this gene


PTH
Gα
AC
ATP
cAMP
PKA
P
CREB
P
CREB
CBP/
p300
CRE
target genes

Coregulators and epigenetic changes regulating vitamin D recep



Assessment of Vitamin D Status

- To date, total serum 25(OH)D, the sum of 25(OH)D3 and 25(OH)D2, is the accepted biomarker of vitamin D status
- **mostly using traditional radioimmunoassay** measurements, vitamin D guidelines issued by major organizations worldwide recommend optimal 25(OH)D levels to be in the range of 50 to 75 nmol/L **(20-30 ng/mL)**
- optimal levels are still debated for several reasons :

1. **Lack of assay standardization**
2. **optimal 25(OH)D level, that is, for whom and for what**
3. **Clinical prospective vs public health prospective**

- differentiate between screening, that is, a public health approach undertaken in the general populations, and testing, that is, targeted testing of high-risk individuals in the clinical setting.

Screening and Testing for Vitamin D Status:

Screening in the general population—public health approach

- **screening** for optimal vitamin D status in the general population **should be avoided** as it is not informative
- considerable economic burden
- several characteristics and pathological conditions in the general population could place individuals at **risk for severe deficits**. These populations, should be recognized

Screening and Testing for Vitamin D Status:

Testing populations at risk of vitamin D deficiency—clinical approach

- Measurement of 25(OH)D has been recommended in patients at risk for deficiency
- Pregnancy ?

Older people

Housebound people
- Disabled people
- Institutionalized people

People working long hours indoors
- Office workers
- Factory or warehouse workers
- Taxi drivers
- Night-shift workers

People with dark skin

Low levels of physical activity

People with a debilitating/chronic disease
- Diabetes
- Chronic kidney disease
- Gastrointestinal malabsorptive syndromes
- Parathyroid disorders
- Liver diseases

Obesity—in particular those with highest levels of waist circumference

Patients after bariatric surgery

People taking medications increasing vitamin D catabolism:
- Phenobarbitone
- Carbamazepine
- Dexamethasone
- Rifampicin
- Nifedipine
- Spironolactone
- Ritonavir
- Cyproterone acetate

Babies of vitamin D-deficient mothers

Screening and Testing for Vitamin D Status:

Testing populations at risk of vitamin D deficiency—clinical approach

Endocrine Society 2024 :

TABLE 2. Indications for 25(OH)D measurement (candidates for screening)

- Rickets
- Osteomalacia
- Osteoporosis
- Chronic kidney disease
- Hepatic failure
- Malabsorption syndromes
  - Cystic fibrosis
  - Inflammatory bowel disease
  - Crohn's disease
  - Bariatric surgery
  - Radiation enteritis
- Hyperparathyroidism
- Medications
  - Antiseizure medications
  - Glucocorticoids
  - AIDS medications
  - Antifungals, *e.g.* ketoconazole
  - Cholestyramine
- African-American and Hispanic children and adults
- Pregnant and lactating women
- Older adults with history of falls
- Older adults with history of nontraumatic fractures
- Obese children and adults (BMI > 30 kg/m^2)
- Granuloma-forming disorders
  - Sarcoidosis
  - Tuberculosis
  - Histoplasmosis
  - Coccidiomycosis
  - Berylliosis
- Some lymphomas

Conditions in which vitamin D status should be evaluated due to reduced synthesis:

- Age >50 years
- Low sun exposure
- Sunscreen
- Air pollution
- Phototype (dark skin)
- Season and latitude

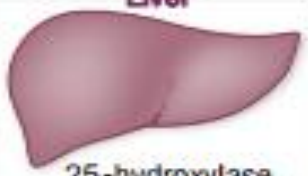
Major source (= 80%) SUNLIGHT

UVB

Skin (Previtamin D)

7-dehydrocholesterol

Cholecalciferol



Liver

25-hydroxylase

25-hydroxyvitamin D

Most used biomarker for Vitamin D status

Minor source (= 20%) DIETARY intake

Ergocalciferol: plants/supplements
Cholecalciferol: fish (cod liver oil), meat, fortified milk, egg yolk, butter

Small Intestine

Conditions in which vitamin D status should be evaluated due to reduced intake:

- Not fortified food
- Restrictive diet
- Gastrointestinal malabsorption: Bariatric surgery, celiac disease, inflammatory bowel diseases

Osteometabolic conditions in which vitamin D status should be evaluated:

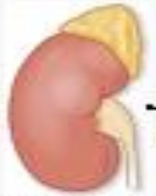
- Parathyroid, kidney diseases and intestinal disorders
- Osteoporosis, osteopenia, skeletal disorders

Clinical conditions in which vitamin D status should be evaluated:

- Low bioavailability: overweight and obese patients
- Increased consumption: patients treated with interfering drugs
- Low 25(OH)D synthesis: Liver dysfunction
- 25(OH)D renal loss or low $1,25(OH)_2D$ synthesis: kidney and parathyroid diseases

Parathyroid hormone

Kidney



1-αhydroxylase

Active form 1,25-dihydroxyvitamin D

- Increases Ca absorption (small intestine)
- Increases urinary Ca and Phos reabsorption
- Increases bone mineralization secondary to the mineral absorptive and resorptive functions

Methods: Assays, Thresholds, and Standardization

- Assay standardization remains a major challenge to interpreting data from various studies evaluating vitamin D and its metabolites and analogues
- The measurements could be obtained by either antibody-based methods (chemiluminescent or immunoenzymatically) or by liquid chromatography–mass spectrometry (LC-MS or LC-MS/MS), with the latter giving more consistent and accurate results

- The mol/L unit should be preferred as the SI standard unit; alternatively, both mol/L and
  ng/mL should be reported
- In 2019,CDC:
  report, 20 immunoassays
  and 17 LC-MS/MS assays were certified as being standardized for serum total 25(OH)D measurement

Assessment of unbound vit D and main metabolites

- For circulating 25(OH)D, it is estimated that approximately 85% to 90% is bound by DBP and 10% to 15% by albumin;
  therefore, free 25(OH)D levels are estimated to be less than 1% of the total and can vary according to DBP and albumin polymorphisms and binding affinity

- The free and not the total 25(OH)D concentration in cell cultures affects a biological response

- While this is harder to assess in vivo,
  some tissues with the megalin/cubilin complex, like the kidney and parathyroid gland, can take up the vitamin D metabolites bound to DBP

Assessment of unbound vit D and main metabolites

- In normal populations, total and free 25(OH)D, as well as free and calculated 25(OH)
  D, are correlated and there is no clear evidence for a need to measure free metabolites in healthy individuals and many clinical setting
- conditions affecting DBP :
- pregnancy
- cirrhosis
- acute illness
- conditions that may affect the affinity of DBP or albumin to its ligands
- aging nursing home residents
  in whom the free concentration is a better assessment than the total

Assessment of unbound vit D and main metabolites

- Measurement of 1,25(OH)2D may contribute to the diagnosis of conditions with low calcitriol levels, such as 1α-hydroxylase deficiency, or those associated with high
  1,25(OH)2D levels, such as hereditary vitamin D–resistant
  rickets, granulomatous conditions (sarcoidosis and tuberculosis)

Assessment of Other Metabolites

- LC-MS/MS techniques
  make it now feasible to measure most of the circulating vitamin D metabolites
- Besides specific clinical situations , a few previous reports have also highlighted a potential role for vitamin D metabolites, in particular of the 24,25 to 25(OH)D ratio, in better-predicting fracture risk as compared to only 25(OH)D levels
- **Infantile hypercalcemia, type 1, caused by defects in CYP24A1** :
- particularly the 25(OH)D to 24,25(OH)2D ratio, has been established as a useful screening tool by groups worldwide. Ratios are elevated from 5 to 25 in normal individuals to more than 80 in infantile hypercalcemia–affected individuals
- Same enzymatic defect can be identified in adults with unexplained 1,25(OH)2D-dependent hypercalcemia
- These individuals present with hypercalcemia, hypercalciuria, kidney stones, and suppressed levels of PTH

Routine documentation of vitamin D metabolites in randomized controlled trial

- In most recent large RCTs, participants were monitored only for health effects and serum 25(OH)D levels
- JAMA study :
- doses of up to 10 000 international units (IU) of vitamin D/day, monitored only 25(OH)D, and reported deleterious effects of the vitamin D on bone mineral density (BMD)
- by reanalyzing the serum from participants in the study for the full vitamin D metabolome including 1,25(OH)2D3, 24,25(OH)2D3, and 1,24,25(OH)3D3, Burt and colleagues found that several vitamin D metabolites, including 1,24,25(OH)3D3 but not 1,25(OH)2D3, were elevated in individuals given the 10,000 IU of vitamin D/day dose, a fact that could explain the bone loss observed at high supplementation rates

Clinical Outcomes of Vitamin D Deficiency

- Skeletal Outcomes
- Extra skeletal Outcomes :
- Cancer
- Cardiovascular risk
- Respiratory effects
- Autoimmune diseases
- Diabetes
- Mortality

Skeletal Outcomes

- Meta-analyses of clinical trials with vitamin D and calcium have demonstrated a decrease in hip and other fractures of around 10% in nursing home residents, **whereas vitamin D alone was not effective**
- As almost all effective trials used a calcium supplement in addition to vitamin D, the effect on BMD of vitamin D supplements alone is difficult to determine, but it is considered to be less than 1%
- and high doses may even be harmful when administered to vitamin D–replete individuals
- In a recent umbrella review of meta-analyses of vitamin D RCTs, the only consistent significant findings were for calcium and vitamin D, and not vitamin D alone, in reducing the risk
  of hip fractures by 16% to 39%, in 8 of 13 meta-analyses, and
  of any fracture, by 5% to 26%, in 8 of 14 meta-analyses

Extra skeletal Outcomes

Study	Participants (n)	Age (mean ± SD), y	Sex (% of women)	Mean BMI	Ethnicity[a] (% White ethnicity)	Serum 25(OH)D, ng/mL		Dose used	Follow-up, y	Primary outcome(s)[c]	Conclusions and comments
						Baseline	Final[b]				
VITAL (117, 125-128)	25 871	67 ± 7	51	28	71	30.8 ± 10	42 ± 10	2000 IU/d + omega-3 1 g/d	5.3	Invasive cancers and major CV events	End point not met, but reduction in total cancer mortality when excluding first 1-2 y of follow-up
										Incidence of metastatic or fatal cancer	VD reduced metastatic or fatal cancers by 17%; strongest reduction in normal BMI
										Two or more falls and falls resulting in a doctor or hospital visit	End point not met
										All incident autoimmune diseases	VD reduced autoimmune diseases by 22%
										Incident total, nonvertebral, and hip fractures	End point not met; enrolled individuals were generally healthy and not selected for VD deficiency, low bone mass, or osteoporosis
D-Health (64, 129, 130)	21 315	69.3	46	28	96.5%	31 ± 10[d]	46 ± 12	60 000 IU/mo	5.7	All-cause mortality	End point not met; VD increased cancer risk when first 2 y of follow-up were excluded
										Risk of falling	End point not met; VD increased risk when BMI <25, but not when BMI ≥25
										Major CV events	End point not met; VD might reduce CV events (small absolute risk difference and CI consistent with null finding); VD reduced myocardial infarction by 19%

Study	Participants (n)	Age (mean ± SD), y	Sex (% of women)	Mean BMI	Ethnicity[a] (% White ethnicity)	Serum 25(OH)D, ng/mL		Dose used	Follow-up, y	Primary outcome(s)[c]	Conclusions and comments
						Baseline	Final[b]				
ViDA (131, 132, 138)	5110	66 ± 8	58	29 ± 5.1	83	27 ± 9[c]	54 ± 16	200 000 IU + 100 000 IU/mo	3.3	Incident CVD and death	End point not met (121); in one substudy, VD lowered central blood pressure in deficient participants
										Fractures and falls	End point not met
										Cancer incidence and mortality	End point not met; daily or weekly dosing for longer period may require further study
FIND (133, 134)	2495	685	43	27 ± 4	100	30 ± 7	40 ± 9 (1600 IU/d arm) 48 ± 9 (3200 IU/d arm)	1600 or 3200 IU/d	4.3	Incident major CVD and invasive cancer	End point not met; study failure possibly due to sufficient VD status in most participants at baseline
										Atrial fibrillation risk	VD reduced atrial fibrillation risk by 27%-32%

Study	Participants (n)	Age (mean ± SD), y	Sex (% of women)	Mean BMI	Ethnicity[a] (% White ethnicity)	Serum 25(OH)D, ng/mL		Dose used	Follow-up, y	Primary outcome(s)[c]	Conclusions and comments
						Baseline	Final[b]				
D2d (135, 136)	2423	60 ± 10	45	32 ± 5	67	28 ± 10	54 ± 15	4000 IU/d	2.5	T2D in adults with prediabetes Development of T2D according to intratrial serum 25(OH)D level	End point not met VD resulting in 25(OH)D level ≥100 nmol/L reduces risk of T2D

Cancer

- No effects of vitamin D supplementation on cancer risk were observed in the large VITAL and ViDA trials, nor the FIND trial using daily dosing in older participants, nor on cancer mortality in the D-Health study, which used monthly dosing —in line with prior trials and MR results
- However, a sub analysis of the VITAL trial showed that vitamin D supplementation could have some minor benefits in individuals with normal BMI
- In addition, several independent trials have suggested, in post hoc analysis, the potential benefits of vitamin D supplementation on cancer mortality, especially when the follow-up is longer than 4 years
- A metanalysis of RCTs suggested that vitamin D supplementation decreased cancer mortality an updated version of this study :
- daily regimens, vitamin D supplementation reduced total cancer mortality SRR 0.87 (0.78-0.96) p=0.007 and incidence SRR 0.79 (0.64-0.90) p=0.001 in normal-weight individual

Cardiovascular risk

- Convergent evidence from MR studies and RCTs suggests that vitamin D supplementation does not decrease the risk of cardiovascular disease (CVD), especially in vitamin D–replete adults
- The FIND trial failed to note a reduction in the number of major CV events:
- however, subsequent exploratory analyses revealed that high-dose vitamin D supplementation might result in benefits in atrial fibrillation prevention in older individuals, even in case of relatively high baseline 25(OH)D concentrations
- D-Health trial:
- the overall rate of major CV—and especially the rate of myocardial infarction and coronary revascularization—was lower in the intervention group compared to the placebo group
- although the absolute risk difference was small, and the CI was consistent with a null finding (hazard ratio 0.91; 95% CI, 0.81-1.01)
- myocardial infarction lower in the intervention group compared to the placebo group (HR 0.81; 95% CI,0.67-0.98)

Respiratory effects

- Serum 25(OH)D levels of less than 25 nmol/L are associated (observationally and genetically) with an increased risk of bacterial pneumonia
- a metanalysis of 25 trials showed a small but significant decrease in the incidence of acute respiratory infections in the vitamin D group compared with the control group when baseline vitamin D status was poor (<25 nmol/L)(<12 ng/ml)
- RCTs show that vitamin D supplementation can benefit infants, toddlers, and preschool children aged 0 to 5 years with a quicker recovery and fewer respiratory symptoms
- Unfortunately, study heterogeneity in terms of design, vitamin D supplementation doses, and duration, along with participant characteristics, make it problematic to pool data and, thus, difficult to draw definitive conclusions

COVID19

- a metanalysis of several observational studies comprising almost 2 million adults suggests that inadequate vitamin D status increases susceptibility to COVID-19 and severe COVID-19, while the association with mortality was less robust
- high risk of bias and heterogeneity

- in the study in Norway: 34700 participants randomized to cod liver oil tablet or none

Duration : 6months

Mean baseline 25(OH)D: 28ng/ml

No reduction of positive COVID 19 PCR tests and serious respiratory infection rate

- In the study in UK : 3100 participants randomized to take either 3200 IU or 800 IU vitamin D daily vs 3100 controls

Duration :6months

mean base 25(OH)D: less than 30 ng/ml

No difference between the two treated groups and untreated control group

COPD & ASTHMA

- A meta-analysis, conversely, found no role for vitamin D supplementation in improving expiratory lung function
- Regarding asthma:
- In a meta analysis of 955 patients ,with asthma needed systematic steroids, there was an overall reduction in exacerbations with incidence rate ratio 0.74, 95% CI (0.56-0.97)
- A subgroup analysis of those with 25(OH) vitD less than 10 ng/ml ,increased effect of vitamin D in reducing exacerbation was seen (RR 0.33,95% CI, 0.11-0.98 P=0.045)
- A post hoc analysis of a New Zealand cardiovascular study (ViDA) with 5110 participants in 775 participants those with copd and asthma no Signiant difference in exacerbations between placebo and VD was found
- However in the 60 participants with serum 25(OH)vitD less than 10 ng/ml exacerbations occurred 7% on vitamin D compared with 70% on placebo(P<0.005)

Autoimmune diseases

- the adaptive immune system is downregulated by 1,25(OH)2D in animal models
- Thus, vitamin D deficiency might predispose to autoimmune diseases
- Observational studies have suggested this effect might apply to humans
- The VITAL RCT showed that vitamin D supplementation2000 IU daily decreased the risk of autoimmune diseases, especially rheumatoid arthritis and polymyalgia rheumatica HR 0.78 95% CI (0.61-0.99 , P=0.05)
- If the last 3 years of the trial considered, the incidence of autoimmune disease was reduced further (HR 0.61, 0.43-0.86 , P=0.005)
- This result could support **the latency** of treatment effect
- 8 large MR studies all agree that genetically predicted lower 25(OH) D levels increased the risk of developing multiple sclerosis either during adolescence or adulthood

Diabetes

- Despite observational studies consistently confirming lower serum 25(OH)D concentrations in patients with T2D or metabolic syndrome , most MR studies have not supported these conclusion
- Two long term randomized trials in over 2900 people to evaluate vitD effect on delay onset of type 2 DM
- 20000 IU every week for 5 years
- 4000 IU daily for 2.5 year
- Median serum 25(OH)D on placebo: 26ng/ml
- Median serum 25(OH)D on VD:51ng/ml
- No effect on preventing DM
- Pos hoc analysis of 103 participant with **vitD less than 10 ng/ml**: significant reduction of type 2 DM (HR 0.38 ,95% CI ,0.18-0.80)

Diabetes

- Furthermore, analysis of the combined results of the D2d (US), Tromsø (Norway), and DPVD (Japan) RCTs
- specifically designed and conducted to test whether vitamin D reduces the risk of diabetes in adults with prediabetes:
- vitamin D supplementation reduced the risk of developing T2D in people with prediabetes not selected for vitamin D deficiency
- An updated individual participant data meta-analysis of the same trials showed that vitamin D reduced the risk of progression from prediabetes to diabetes by 15% , HR:0.85 (0.75-0.96)
- Also, vitamin D increased the likelihood of regression to normal glucose regulation by 30%, RR :1.30 (1.16-1.46) with no evidence of risk
- In additional analyses, participants in the vitamin D group who maintained interatrial blood 25(OH)D of 50 ng/mL or greater (≥125 nmol/L) had a 76% risk reduction in new-onset diabetes compared to those who maintained blood 25(OH)D of 20 to 29 ng/mL
(50-75 nmol/L) HR : 0.24 (0.16-0.36)

Diabetes

- the evidence from large-scale MR studies and RCTs is convergent and **does not support** vitamin D supplementation to prevent T2D in the **general population**

- However, vitamin D supplementation **benefits** those with **prediabetes** and a predisposition to T2D

Mortality

- Observational data have repeatedly linked poor vitamin D status with increased mortality
- The positive but small effect of vitamin D on mortality was confirmed by a recent umbrella review of observational, randomized, and MR studies
- In conclusion, if vitamin D supplementation benefits extra skeletal health outcomes and major diseases, it is likely to have some effects on mortality, especially in older adults with poor vitamin D status, but not in younger, replete individuals

Summary of Vitamin D Deficiency-associated Clinical Outcomes

- when it comes to vitamin D, it is advisable to “giveth to those who needeth”
- In fact, the benefit-to-risk ratio for vitamin D depends on the target population and medical condition
- Nonetheless, RCTs, MR studies, and metanalyses suggest a link between vitamin D status with **the immune system** and **diabetes**, as well as fleeting effects on some **CV events** and some benefits on **mortality** risk when vitamin D3 is used.

Vitamin D Supplementation

- **Dosing Regimens :**
- cholecalciferol, and other formulations such as ergocalciferol, eldecalcitol, calcifediol, etc are also available in a pill: It is expressed as µg or IU (where 10 µg is 400 IU)
- Daily doses are generally preferred when vitamin D replacement is considered necessary
- The effect of a given dose on changing blood 25(OH)D varies considerably from person to person due to many factors, such as body weight, absorption, diet, degree of adiposity, CYP2R1 activity, DBP
- National Academy of Medicine : 400 to 800 IU per day, and the tolerable upper intake level at 4000 IU per day

Vitamin D Supplementation

- **Dosing Regimens :**

- pediatric setting: Infants and children have different upper tolerance limits compared to adults
- To maintain a desirable 25(OH)D concentration, the 2010 IOM guidelines: recommend 600 IU/d (15 μg) for children, adolescents, and adults
- and 400 IU/d (10 μg) for infants
- ES guidelines: recommend 400 to 1000 IU/day (10-25 μg) for infants aged up to 1 year
- 600 to 1000 IU/day (15-25 μg) for children older than 1 year to treat and prevent vitamin D deficiency

Vitamin D Supplementation

- **Dosing Regimens :**

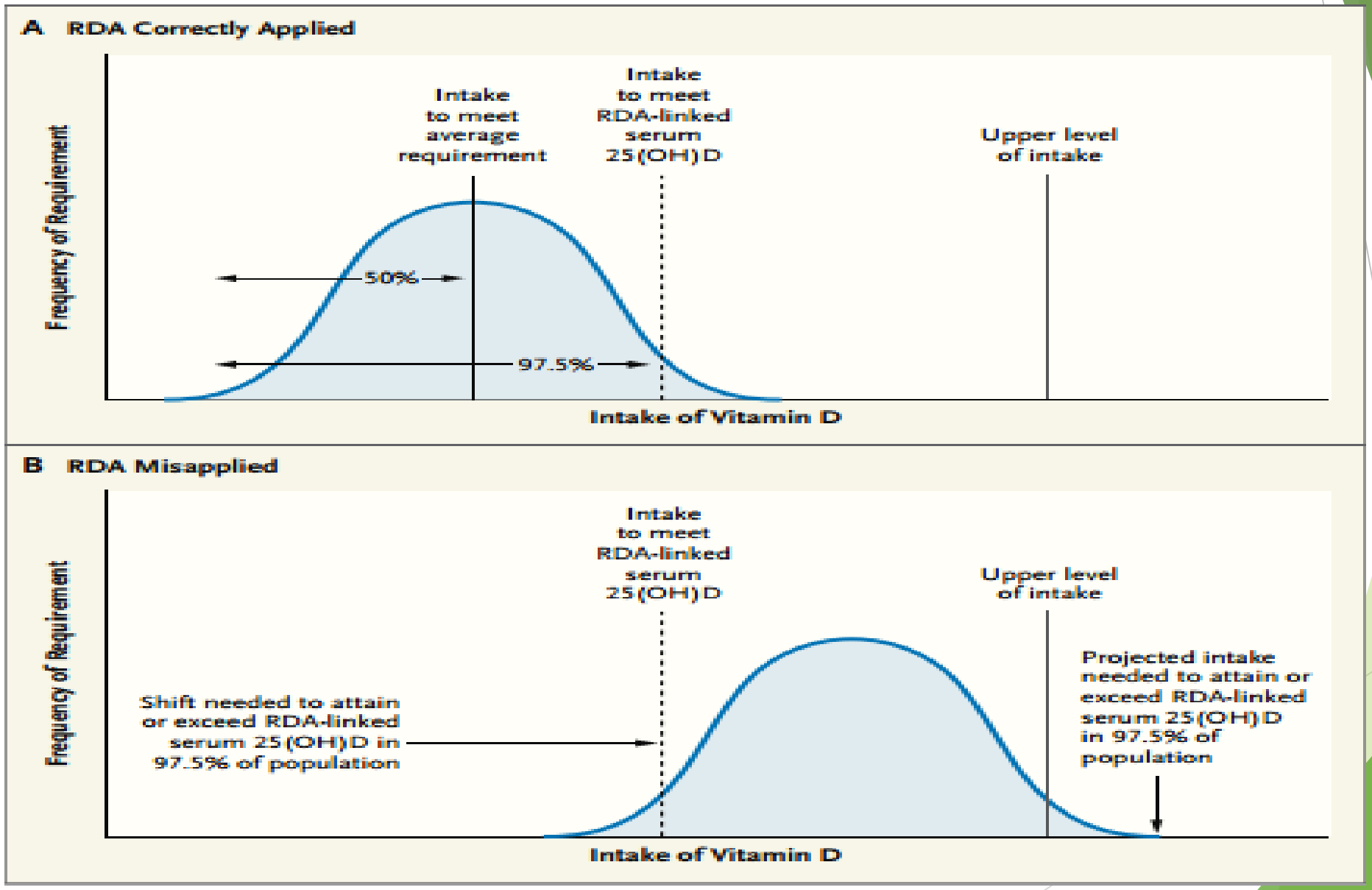
- Obese and overweight individuals requiring 2.6 and 1.47 times higher supplementation
- ES guidelines :
  vitamin D dosage for obese people is “three times” greater than the recommended dose for individuals with normal body weight

Life stage group	IOM recommendations				Committee recommendations for patients at risk for vitamin D deficiency	
	AI	EAR	RDA	UL	Daily requirement	UL
Infants						
0 to 6 months	400 IU (10 μg)			1,000 IU (25 μg)	400–1,000 IU	2,000 IU
6 to 12 months	400 IU (10 μg)			1,500 IU (38 μg)	400–1,000 IU	2,000 IU
Children						
1–3 yr		400 IU (10 μg)	600 IU (15 μg)	2,500 IU (63 μg)	600–1,000 IU	4,000 IU
4–8 yr		400 IU (10 μg)	600 IU (15 μg)	3,000 IU (75 μg)	600–1,000 IU	4,000 IU
Males						
9–13 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
51–70 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
>70 yr		400 IU (10 μg)	800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
Females						
9–13 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
51–70 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
>70 yr		400 IU (10 μg)	800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
Pregnancy						
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
Lactation[a]						
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU

AI, Adequate intake; EAR, estimated average requirement; UL, tolerable upper intake level.

[a] Mother's requirement, 4,000–6,000 IU/d (mother's intake for infant's requirement if infant is not receiving 400 IU/d).

IOM concept about RDA



Vitamin D Supplementation

- **Daily supplementation** :
- In a recent RCT comparing 3 different dosing regimens in vitamin D–deficient participants with similar total end-of-study cumulative doses:
- (D3 daily 10 000 IU 8 weeks,then 1000 IU for 4 weeks;
- 50 000 IU weekly for 12 weeks;
- 100 000 IU every 2 weeks for 12 weeks)
- the group receiving the daily supplementation was the quickest to reach sufficiency (<2 weeks, although receiving a higher cumulative dose in the first 8 weeks when compared to the other 2 arms)
- Importantly, daily administration was associated with higher systemic exposure to 25(OH)D (greater area under the curve, +23% and +27% compared to weekly and biweekly administration, respectively), even when corrected for the cumulative dose
- The greater 25(OH)D exposure of daily regimens could be due to lower activation of the 24-hydroxylase enzyme (CYP24A1)

Vitamin D Supplementation

- **Daily supplementation** :
- Greater 25(OH)D exposure and lesser 24-hydroxylase activity might be the rationale behind the potential extra skeletal benefits of cholecalciferol supplementation
- metanalysis of 12 RCTs by Keum et al found that the reduction in cancer mortality after vitamin D supplementation was largely attributable to interventions with daily dosing (as opposed to infrequent bolus dosing)
- Secondary analyses of the VITAL trial giving 2000 IU/day of cholecalciferol found
  a significant reduction in advanced cancers (metastatic or fatal), especially among those with normal BMI
- However, the opposite was seen with monthly dosing in the D-Health trial, where the risk of death from cancer was increase

Vitamin D Supplementation

- **Weekly and monthly regimens** :
- As compared with a daily regimen, a bolus dose is associated with a higher 24,25(OH)2D level and a higher 24,25(OH)2D to 25(OH)D ratio
- Monthly regimens have been tested in several large trials with multiple outcomes Compared to a placebo, 100 000 IU monthly did not influence the risk of CVD, falls, fracture, or cancer, and lung or arterial functions in vitamin D–replete individual
- In the D-Health trial including more than 21 000 individuals, with 24% of them having a 25(OH)D level less than 50 nmol/L, 60 000 IU monthly did not influence all-cause
  mortality but was associated with a higher risk of falls in those with a BMI of less than 25
- This observation was in agreement with another trial in which a higher percentage of fallers was detected with 60 000 IU/month compared to 24 000 IU/month over 1 year

Vitamin D Supplementation

- **Weekly and monthly regimens** :
- Overall, trials with weekly or monthly vitamin D supplementation regimens did not show significant effects on clinical variables

- Currently, there is no evidence of a superiority in the benefit/risk ratio of weekly or monthly vitamin D regimens over daily supplementation.

Longer intervals

- studies (500 000 IU every year /150 000 IU every 3 months did not show a reduction in hip/vertebral/nonvertebral/total fracture incidence

- Regarding the relation between long-term intervals of vitamin D administration and CVD risk, falls, and fracture outcomes in older and community-dwelling people, in a systematic review with meta-analysis, Barbarawi et al did not found significant results favoring vitamin D intervention (100 000 IU every 4 months, 500000 IU yearly in preventing falls, fractures, or CVDs

Summary of Vitamin D Dosing Regimens

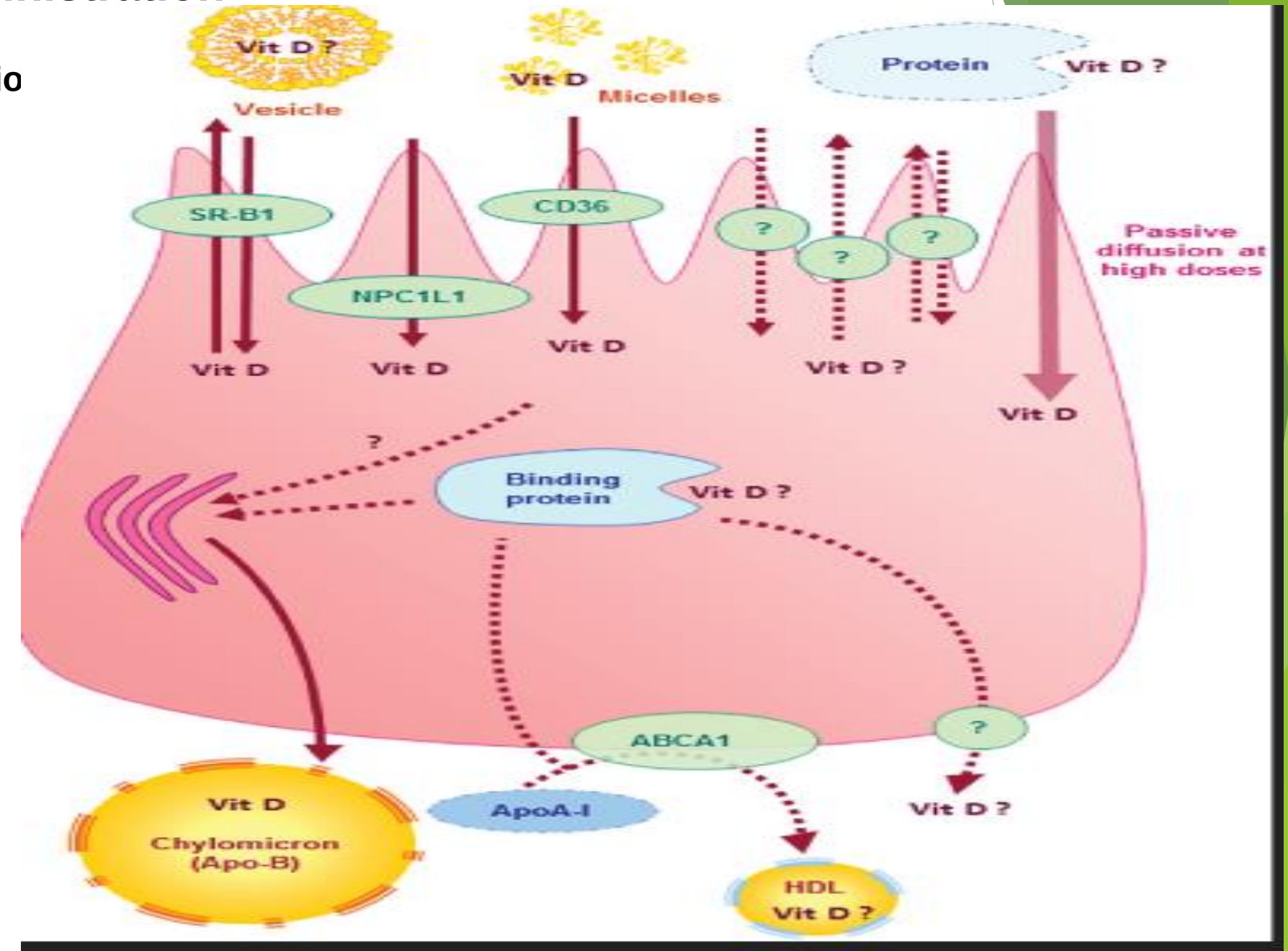
- In conclusion, one of the major justifications for longer intervals with high doses in vitamin D administration, namely, to address low compliance with more frequent regimens, is controversial
- The rationale gains support in children and adolescents rather than in older individuals
- cited meta-analyses underscored the point that there is no evidence of efficacy in intermittent high-dose and longer intervals of vitamin D administration in reducing fracture rate, falls, CV events, or infectious diseases
- An increase in falls in older individuals has been observed with large, intermittent dosing

Routes of Administration

- **Oral administration** :
- Cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2):
- fat-soluble vitamins that are absorbed in the small intestine
- lipophilic compounds
- their absorption is similar to the absorption of lipids
- Vitamin D is incorporated into micelles with biliary salts on the micelle surface
- On average, about 80% of vitamin D is absorbed

Routes of Administration

- Oral administratio



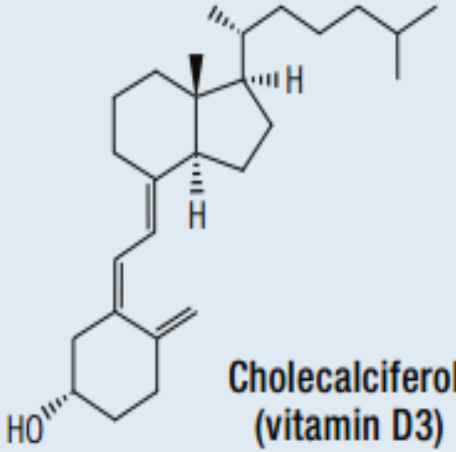
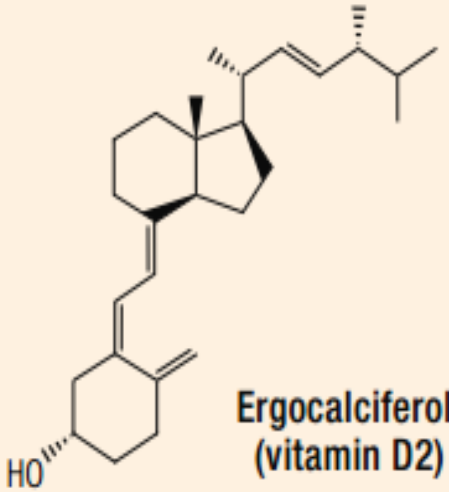
Routes of Administration

- **Oral administration:**
- Cholecalciferol and ergocalciferol are both rapidly absorbed, and the plasma levels peak after about 24 hours of ingestion
- Bariatric surgery and intestinal malabsorption syndromes that reduce fat absorption:
- inflammatory bowel diseases
- cystic fibrosis
- and severe cholestasis
- drugs : orlistat , olestra
- Vitamin D supplements are available in different vehicles, such as oil-containing gel capsules, oily drops, and hard powder tablets
- better absorption in powder-based vehicle than from an oil-based vehicle in cases of intestinal fat malabsorption, such as in cystic fibrosis

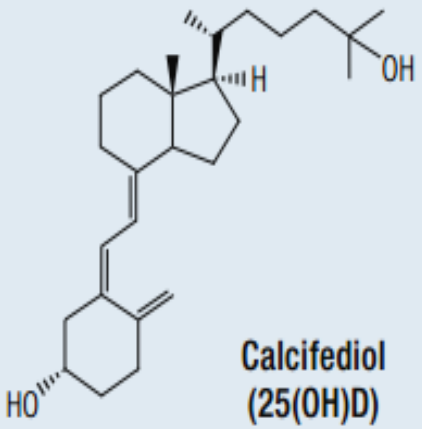
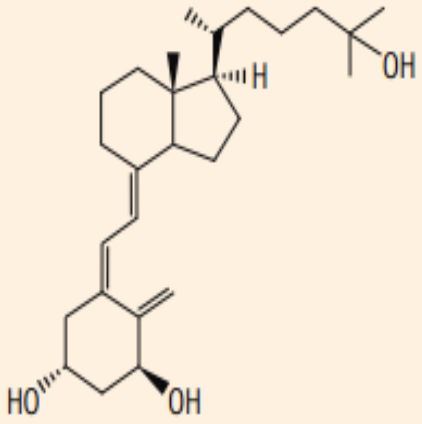
Routes of Administration

- **Parenteral administration** :
- Parenteral administration of intermittent vitamin D boluses may be indicated in patients with hypovitaminosis D who are not suitable for oral intake or with intestinal malabsorptive diseases, including inflammatory bowel disease, celiac disease, pancreatic insufficiency, short-bowel syndrome, and post bariatric surgery
- Intramuscular cholecalciferol may be the preferred form of vitamin D to be used in these clinical settings
- useful in clinical conditions when rapid correction of hypovitaminosis D is unnecessary and for long-term maintenance of adequate serum vitamin D levels, as in some older patients,
  to improve their adherence to vitamin D supplementation.
- large intramuscular boluses (300 000 IU) induce unwanted effects such as an increase in
  falls and fracture events or enhance bone turnover
- There is a consensus to administer vitamin D **boluses not higher than 100 000 IU**

Different Forms of Vitamin D Supplementation

Vitamin D form	Circulating half-life	Features	When to use it
 Cholecalciferol (vitamin D3)	Around 1 day (longer functional half-life in correlation with its slow release from the adipose tissue)	• Native form of human- and animal-produced vitamin D • Lipophilic, stored in fat and released on need • Useful in clinical practice as it renders possible intermittent administration regimes • Wide safety range thanks to the predicted mechanisms regulating its hydroxylation	Most clinical situations where a vitamin D deficiency must be addressed (see below for exceptions)
 Ergocalciferol (vitamin D2)	Around 2 days	• Inferior to cholecalciferol in increasing 25(OH)D serum levels • Risk of over- or under-estimation of total 25(OH)D in the presence of substantial amounts of 25(OH)D2 with subsequent risk of vitamin D toxicity in case of dose increments • Widely prescribed in the USA in high doses (50,000 IU) • High doses alter vitamin D metabolism, increasing 24 hydroxylase activity	Only in cases of patients' ethical concern (e.g., vegetarianism, veganism, others). However, vegan D3 supplements (made from lichen) are available and should be considered instead of D2 supplements

Different Forms of Vitamin D Supplementation

 **Calcifediol (25(OH)D)**	2-3 weeks	• Hydrophilic, thus higher solubility in organic solvents, less sequestration in adipose tissue, smaller distribution volume and shorter half-life compared to cholecalciferol • Fast increase in 25(OH)D serum levels along with PTH suppression • Easier to manage than cholecalciferol in case of toxicity • More efficient internalization in cells expressing the megalin-cubilin system	Malabsorption syndromes, obesity, CYP2R1 dysfunction, or in situations in which a quick attainment of vitamin D sufficiency is desirable
 **Calcitriol (1,25(OH)2D)**	5-8 hours	• Promotes active intestinal calcium absorption and suppresses PTH secretion • Increases the activity of the CYP24A1, which stimulates the degradation of 25(OH)D • Risk of hypercalcemia and hypercalciuria • To be administered daily or in lower doses distributed over a 24-hour period	As a hormone replacement for patients with limited/absent renal tubular 1-α-hydroxylase activity; vitamin D resistant rickets type 1, X-linked hypophosphataemic rickets, chronic hypoparathyroidism, as an alternative to the use of the native missing hormone PTH, and moderate-to-severe kidney failure Consider replacing it with analogs with less calcemic activity (maxacalcitol; falecalcitriol; paricalcitol; doxercalciferol)

Ergocalciferol

- Ergocalciferol does exist in nature (mainly in plants and fungi)
- The 2 forms of vitamin D, cholecalciferol (D3) and ergocalciferol (D2), are often used interchangeably as supplementation or treatment of vitamin D deficiency as, historically, vitamins D2 and D3 were considered equally effective in treating ricket
- Challenges to 25(OH)D measurement are widely recognized
- The presence of 2 circulating 25(OH)D forms, 25(OH)D3 and 25(OH)D2, adds additional challenges, notably for automated immunoassays
- it is possible that the antibodies used in immunoassays may not detect 25(OH)D2 and 25(OH)D3 equally, and the proprietary approach to releasing 25(OH)D from DBP may not liberate the 2 forms equally
- In addition to assay issues, widespread use of intermittent high dose ergocalciferol (“bolus” therapy) appears to alter vitamin D metabolism, with increased 24-hydroxylase activity

Ergocalciferol

- To summarize, vitamins D2 and D3 are not equivalent in raising circulating 25(OH)D, and bolus dosing may have adverse effects on vitamin D metabolism and clinical outcomes.
- As such, it is to be expected that calls for the use of only cholecalciferol and avoidance of ergocalciferol have been and continue to be published
- Recent osteoporosis-treatment guidance advising cholecalciferol over ergocalciferol

Calcifediol

- Calcifediol is the intermediate metabolite between cholecalciferol and calcitriol
- hydrophilic properties
- less sequestration in adipose tissue, smaller distribution volume
- and shorter half-life when compared to cholecalciferol
- absorbed via the venous portal system and thus quickly increases circulating concentrations of 25(OH)D3
- In contrast to cholecalciferol, which is mostly stored in fat tissue, 25(OH)D tends to be more evenly distributed throughout the body (20% in muscle, 30% in circulation, 35% in fat, and 15% elsewhere)
- lead to predictable 25(OH)D levels
- effective PTH suppression
- In cases of toxicity, this form of vitamin D is easier to manage than cholecalciferol

Calcifediol

- The clinical situations that make use of calcifediol attractive :
- obesity
- hepatic failure
- patients with inactivating mutations of genes encoding CYP2R1 (the principal enzyme that is responsible for vitamin D 25-hydroxylation)
- or patients taking drugs that could influence the activity of cytochrome enzymes (ie, antiretroviral or antitubercular)
- Calcifediol was shown to have the same bioavailability in healthy adults with differing BMI and adults with intestinal malabsorption compared to controls

- New extended-release calcifediol formulations are more effective than cholecalciferol in raising serum 25(OH)D levels even in overweight nonanalytic CKD patients with secondary hyperparathyroidism

Calcitriol

- active hormonal form of vitamin D and the natural VDR ligand
- active intestinal calcium absorption and suppresses PTH secretion
- short half-life of around 5 to 8 hours
- administered daily and sometimes in lower doses distributed over a 24-hour period
- requires careful monitoring
- Calcitriol increases the activity of CYP24A1
- more significant incidence of adverse events such as hypercalcemia and hypercalciuria
- there is consensus that calcitriol use should be limited to:
- hormone replacement for patients with limited/absent renal tubular 1-α-hydroxylase activity,
- treat patients with vitamin D–resistant rickets type 1
- indications are X-linked hypophosphatemia rickets
- chronic hypoparathyroidism
- moderate-to severe kidney failure when calcitriol production is impaired or to suppress excessive PTH secretion

Calcitriol

- as calcitriol use is associated with frequent hypercalcemia, its use could be replaced by analogues with less calcemic activity approved for use in patients with secondary hyperparathyroidism in renal failure, in particular maxacalcitol (22-oxa-1,25(OH)2D3) and falecalcitriol (1,25(OH)2-26,27-F6-D3), which are currently available in
  Japan, and paricalcitol (19-nor-1,25(OH)2D2) and doxercalciferol (1α(OH)D2), available in the United States
- **guidelines suggest that vitamin D supplementation is advised in patients with chronic**
  hypoparathyroidism, chronic kidney failure, and low vitamin D status in addition to receiving therapeutic doses of calcitriol

Vitamin D toxicity

- rare due to the wide therapeutic index of vitamin D VDT is defined by a biochemical phenotype with
markedly elevated calcifediol concentrations (>150 ng/mL or >375 nmol/L)
- In healthy individuals, hypervitaminosis D is usually defend as “exogenous” as it develops after uncontrolled use of megadose of vitamin D
- excessive production of calcitriol in granulomatous disorders, lymphomas, primary hyperparathyroidism, and idiopathic infantile hypercalcemia results in “endogenous” hypervitaminosis D
- Calcitriol levels may be in the normal reference range
or even reduced in exogenous VDT while elevated in endogenous VDT
- Pathogenetically, hypercalcemia is a consequence of high calcifediol levels in exogenous VDT (with calcifediol at pharmacological concentrations overcoming VDR affinity disadvantages and/or displacing 1,25(OH) D2 from DBP

Vitamin D toxicity

- **Exogenous factors that interact with VDT:**
- dosage
- calcium in the diet or as a supplement,
- vitamin D intake with the diet
- social status (ie, neglected patients)
- artificial UV light treatment sessions
- time of exposure
- **Endogenous risk factors:**
- age
- sex
- vitamin D status
- hypersensitivity syndrome
- pharmacogenetics of the vitamin D response and metabolism

Monitoring vitamin D status during treatment

- calculated that the cholecalciferol loading dose required to reach the serum 25(OH)D target level of 75 nmol/L can be calculated as dose (IU) = 40 × [75 - serum 25(OH)
  D] × body weight
- cholecalciferol can maintain physiological 25(OH)D serum levels above 30 ng/mL (75 nmol/L) but below 50 ng/mL (125 nmol/L) for a long time, regardless of whether the dosage given is daily or intermittent
- Routine monitoring of 25(OH)D levels is generally **unnecessary** for patients on long-term maintenance vitamin D doses of up to at least
  2000 IU/day

Monitoring vitamin D status during treatment

- Retesting after 8 to 12 weeks from the start of supplementation may be appropriate when **poor compliance** is suspected, in case of **symptoms** suggestive of vitamin D deficiency, and for patients **at risk of persistent 25(OH)D level below 30 ng/mL :**
- institutionalized or hospitalized individuals
- people in whom vitamin D therapy uncovers subclinical primary hyperparathyroidism
- obese individuals
- individuals undergoing bariatric surgery
- individuals who use of certain concomitant medications (eg, anticonvulsant medications, glucocorticoids)
- and patients with malabsorption, including inflammatory bowel disease and celiac disease
- **For patients on potent antiresorptive agents(eg, denosumab or zoledronic acid), vitamin D levels should be checked annually per protocol**

Conclusions

- Vitamin D metabolism involves a different extensive panel of enzymes
- the VDR has been demonstrated to act as a key role transcription factor in most cells and can regulate a plethora of gene
- assessing a distinctive pattern of noncanonical vitamin D metabolites may allow us to better characterize different pathological conditions related to vitamin D metabolism that do not depend only on reduced solar exposure or vitamin D diet intake
- Another critical issue is the lack of an accepted laboratory test assay standardization, and this prevents a proper interpretation of data reported by different studies
- Thus, 25(OH)D laboratory assays should be monitored in their performance through external quality assessment plans providing target reference values from standardized
measurement procedures

Conclusions

- More recently, the interest in the putative extra skeletal effects of vitamin D have resulted in several clinical trials addressing vitamin D's influence on cancer and CV risk, respiratory effects, autoimmune diseases, diabetes, and mortality
- their null results were mainly related to the enrollment of vitamin **D–replete adults** in whom benefit would be unlikely and **the inhomogeneous** methodologies in vitamin D supplementation with different forms, metabolites, and doses
- Indeed, subsequent secondary analyses have progressively shown that vitamin D might be useful in reducing cancer incidence and mortality in the long term, in reducing autoimmune diseases and CV events (in particular central arterial hypertension, myocardial infarction, and atrial fibrillation) occurrence, and the development of diabetes from prediabetes
- for vitamin D supplementation, oral administration is the preferred route
- Cholecalciferol remains the preferred choice
- 400-800 IU per day
- No need to monitoring serum 25(OH)D in the healthy population

thanks for your attention