D vitamīna deficīta ārstēšanas barjeras Latvijā

INĀRA ĀDAMSONE, nefroloģe

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Rīgas Stradiņa universitāte

LOKMSA

PAULA STRADIŅA KLĪNISKĀ UNIVERSITĀTES SLIMNĪCA

RĪGAS STRADIŅA UNIVERSITĀTE

Latvijas Osteoporozes un kaulu metabolo slimību asociācija

Ievads

- D vitamīnam ir būtisks loma kaulu un minerālvielu metabolismā un tas ir efektīvs līdzeklis rahīta un osteomalācijas profilaksē un terapijā, kā arī ilgus gadus tiek uzskatīts par neatņemamu osteoporozes terapijas sastāvdaļu
- Taču ņemot vērā to, ka D vitamīna receptorus (VDR) sastop praktiski visos audos un šūnās, ir daudz pētījumu arī par potenciāliem D vitamīna ārpusskeleta efektiem
  - Epidemioloģiskie pētījumi norāda, ka zems D vitamīna līmenis saistīts ar daudzām akūtām un hroniskām saslimšanām. Tas raisījis interesi par D vitamīna pielietojumu daudzās medicīnas jomās
  - Tomēr RCT lielā vairumā gadījumu nav pierādījuši būtisku D vitamīna papildus lietošanas efektu uz dažādiem ar šīm slimībām saistītiem galaiznākumiem
- Sekas – šobrīd daudz pretrunīgu zinātnisku diskusiju un dažādu pieeju klīniskajā praksē un sabiedrības veselības politikā attiecībā uz D vitamīna noteikšanu un izmantošanu terapijā

Pilz S, et al. Endocr Connect. 2019; 8(2): R27–R43

D vitamīna deficīta ārstēšana – jautājumi

- D vitamīna noteikšana –
  - Kuru metabolītu noteikt?
  - Kam noteikt?
- Kādam jābūt D vitamīna līmenim?
- Kā nozīmēt D vitamīna terapiju?
  - Kas to dara?
  - Orāli vai parenterāli?
  - Ikdienas režīmā vai intermitējoši?
  - Ar kādu devu uzsākt ārstēšanu?
  - Kā turpināt?
- Kā monitorēt D vitamīna efektu?

Endocrine CONNECTIONS

S Pilz *et al.* | Vitamin D testing and treatment | 8:2 | R27–R43

REVIEW

Vitamin D testing and treatment: a narrative review of current evidence

Stefan Pilz[1], Armin Zittermann[2], Christian Trummer[1], Verena Theiler-Schwetz[1], Elisabeth Lerchbaum[1], Martin H Keppel[3], Martin R Grübler[4], Winfried März[5,6,7] and **Marlene Pandis[1]**

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Endocrine Connections
(2019) **8**, R27–R43

endocrine reviews

Endocr Rev. 2019 Aug; 40(4): 1109–1151.
Published online 2018 Oct 12. doi: 10.1210/er.2018-00126: 10.1210/er.2018-00126

PMCID: PMC6626501
PMID: 30321335

Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions

Roger Bouillon,[1] Claudio Marcocci,[2] Geert Carmeliet,[1] Daniel Bikle,[3] John H White,[4] Bess Dawson-Hughes,[5] Paul Lips,[6] Craig F Munns,[7,8] Marise Lazaretti-Castro,[9] Andrea Giustina,[10] and John Bilezikian[11]

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JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

ENDOCRINE SOCIETY

J Clin Endocrinol Metab. 2019 Feb 1;104(2):234-240. doi: 10.1210/jc.2018-01414.

Controversies in Vitamin D: Summary Statement From an International Conference.

Giustina A[1], Adler RA[2], Binkley N[3], Bouillon R[4], Ebeling PR[5], Lazaretti-Castro M[6], Marcocci C[7], Rizzoli R[8], Sempos CT[9], Bilezikian JP[10].

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10 Endocrinology Division, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York.

National Osteoporosis Society

Vitamin D and Bone Health:

A Practical Clinical Guideline for Patient Management

Authors: Prof. Roger Francis (Chair), Dr. Terry Aspray, Prof. William Fraser, Prof. Helen Macd Dr. Sanjeev Patel, Dr. Alexandra Mavroeidi, Dr Schoenmakers, Prof. Mike Stone.

Publication date: December 2018

frontiers in Endocrinology

Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

Michael F. Holick, Neil C. Binkley, Heike A. Bischoff-Ferrari, Catherine M. Gordon, David A. Hanley, Robert P. Heaney, M. Hassan Murad, and Connie M. Weaver

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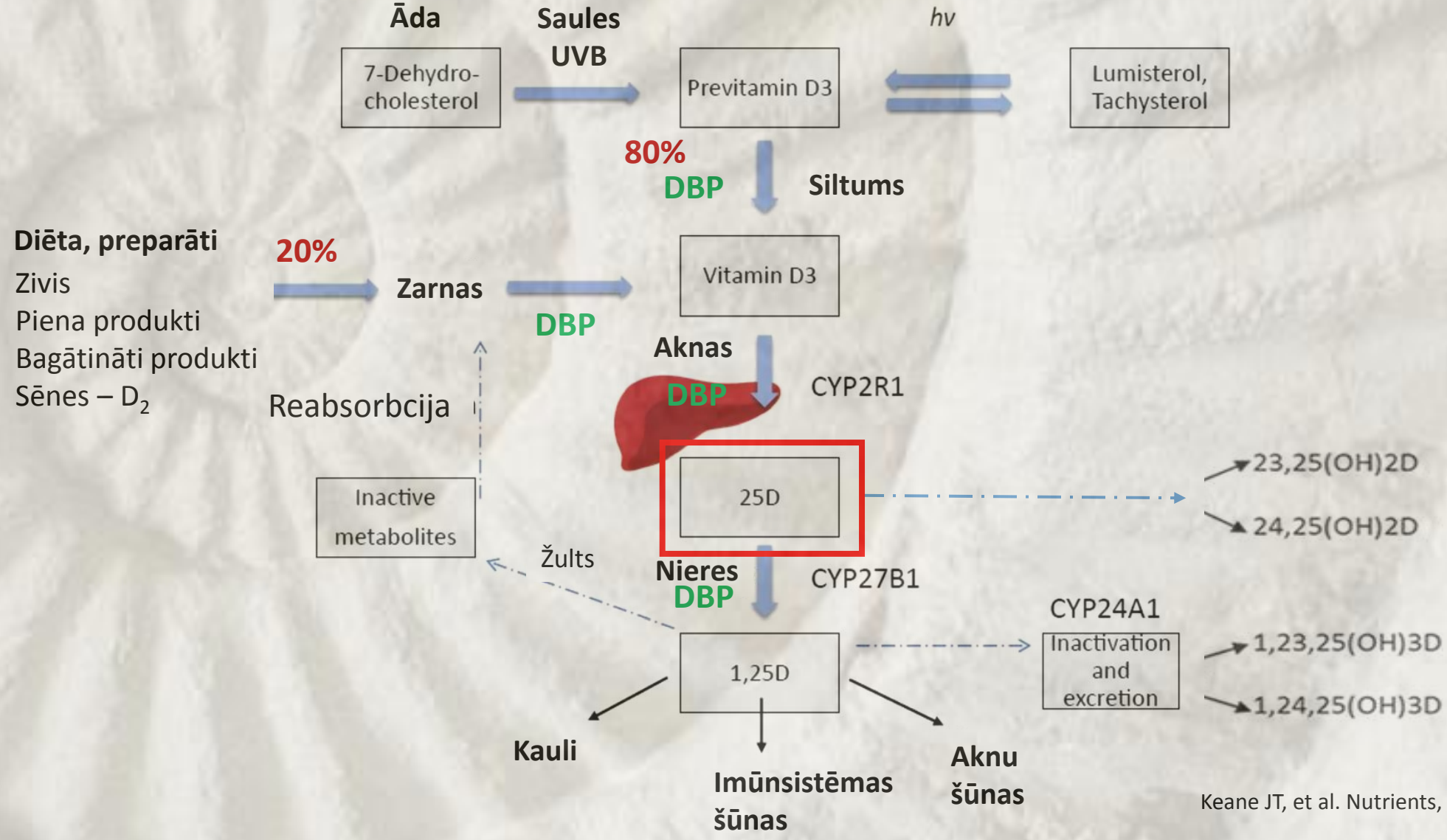
J Clin Endocrinol Metab, July 2011, 96(7):1911–1930

Vitamin D Supplementation Guidelines for General Population and Groups at Risk of Vitamin D Deficiency in Poland—Recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel With Participation of National Specialist Consultants and Representatives of Scientific Societies—2018 Update

Agnieszka Rusińska[1†], Paweł Płudowski[2], Mieczysław Walczak[3], Maria K. Borszewska-Kornacka[4], Artur Bossowski[5], Danuta Chlebna-Sokół[1], Justyna Czech-Kowalska[6], Anna Dobrzańska[6], Edward Franek[7], Ewa Helwich[8], Teresa Jackowska[9], Maria A. Kalina[10], Jerzy Konstantynowicz[11], Janusz Książyk[12], Andrzej Lewiński[13], Jacek Łukaszkiewicz[14], Ewa Marcinowska-Suchowierska[15], Artur Mazur[16], Izabela Michałus[1], Jarosław Peregud-Pogorzelski[17], Hanna Romanowska[3], Marek Ruchała[18], Piotr Socha[19], Mieczysław Szalecki[20,21], Mirosław Wielgoś[22], Danuta Zwolińska[23] and Arkadiusz Zygmunt[13]*

Front. Endocrinol., 31 May 2018

Kuru D vitamīna formu noteikt?



Keane JT, et al. Nutrients, 2018; **10:** 496

Kuru D vitamīna formu noteikt?

- D vitamīna pietiekamību klasificē, balstoties uz **25(OH)D līmeņa noteikšanu serumā**
  - Salīdzinot ar D vitamīnu, augstāka koncentrācija serumā,
  - Ilgāks pussabrukšanas periods (3 nedēļas vs 1 diena),
  - Atspoguļo krājumus, kas nāk no visiem D vitamīna avotiem (āda, uzturs)
- Serumā cirkulē **25(OH)D_3 un 25(OH)D_2** metabolīti. Svarīgi noteikt abus. Laboratorijas reaģenti nosaka **kopējo 25(OH)D līmeni serumā** (25(OH)D3 + 25(OH)D2)
- Asinsritē D vitamīna metabolīti cirkulē piesaistīti D vitamīna saistītājolbaltumam (nedaudz – arī albumīnam, lipoproteīniem). < 1% - brīvais D vitamīns. Taču vairumā šūnu D vitamīna metabolīti piesaistās VDR tieši kā brīvais D vitamīns
- Tāpēc dažos gadījumos var būt lietderīga **brīvā 25(OH)D** noteikšana (kad D vitamīna saistītājolbaltuma daudzums ir izmainīts – aknu ciroze, grūtniecība, hormonālās kontracepcijas lietošana)
- **1,25(OH)$_2$D** (kalcitriols) – aktīvā jeb hormonālā D vitamīna forma, kas veidojas 25(OH)D vitamīna renālas hidroksilācijas rezultātā. D vitamīna forma, kurai piemīt vislielākā sasaistes spēja ar VDR audos.
- **1,25(OH)$_2$D līmenis precīzi neatspoguļo D vitamīna krājumus organismā**, jo tā koncentrācija serumā tikai nelielā mērā atkarīga no pieejamā substrāta – 25(OH)D. Vairāk to ietekmē minerālu vielmaiņu regulējošās substances – PTH, fosfors, FGF-23 un nieru funkcija. Īss pussabrukšanas periods (4 stundas), 1000x zemāka koncentrācija nekā 25(OH)D
- **D vitamīna aktīvo formu preparātu (alfakalcidols, kalcitriols, parikalcitols) lietošanas gadījumā 25(OH)D līmenis neatspoguļo D vitamīna pietiekamību**. Šo preparātu terapijas efektivitāti kontrolē, nosakot PTH un Ca (serumā, urīnā)

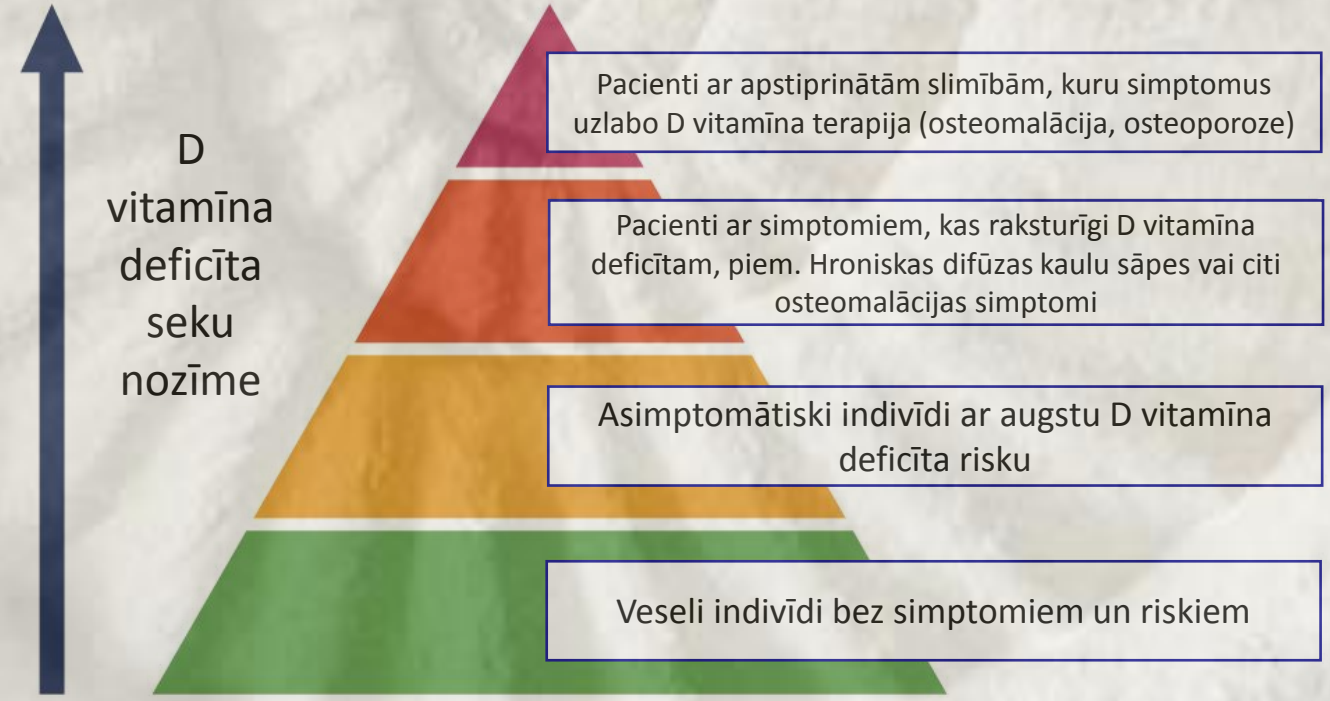
Kam noteikt 1.25$(OH)_2$D līmeni?

- Nieru slimības ar HNS
  - HNS 4 un 5 pacientiem ir pazemināts 1,25$(OH)_2$ D līmenis, taču pat šiem slimniekiem 25(OH)D ir labāks D vitamīna krājumu indikators, bet PTH – labāks Ca vielmaiņas traucējumu marķieris
- Hiperparatireoze, hipertireoze
- Neizskaidrojama hiperkalcēmija (meklējot granulomatozas slimības – sarkoidozi, tuberkulozi u.c. vai limfomu)
- Aizdomas par "ģenētisku" rahītu bērnībā
- Aizdomas par audzēja izraisītu skeleta bojājumu
- Daži nierakmeņu un hiperkalciūrijas varianti
- Zinātniski pētījumi
- Norma: 15-20 līdz 50-60 pg/ml

Dirks NF, et al.Nutrients. 2018 Apr; 10(4): 482

Kam noteikt D vitamīnu?

- Daudzu profesionālu organizāciju un ekspertu viedoklis – vispārējs D vitamīna deficīta skrīnings populācijā (asimptomātiskiem zema riska pacientiem) **nav jāveic**
- Nav vienota viedokļa par to, kurām augsta D vitamīna deficīta riska grupām šis skrīnings būtu jāveic



Bouillon R, et al. Endocr Rev, 2019;40:1109-1151
Giustina A, et al. J Clin Endocrinol Metab, 2019;104:234-240
Dawson-Hughes B. Vitamin D deficiency in adults. UpToDate.com; 2019

Kam noteikt 25(OH)D līmeni?

- Rahīts
- Osteomalācija
- Osteoporoze
- Hroniska nieru slimība
- Aknu mazspēja
- Malabsorbcijas sindromi
  - Cistiskā fibroze
  - Ulcerozs kolīts
  - Krona slimība
  - Pēc bariatriskas ķirurģijas
  - Radiācijas enterīts
- Hiperparatireoze
- Vecāki cilvēki ar kritieniem anamnēzē
- Vecāki cilvēki ar netraumātiskiem lūzumiem anamnēzē
- Afroamerikāņu un spāņu izcelsmes bērni un pieaugušie
- Sievietes - grūtnieces un zīdītājas
- Adipozi bērni un pieaugušie (ĶMI 30 kg/m^2)

- Medikamenti
  - Antikonvulsanti
  - Glikokortikoīdi
  - AIDS medikamenti
  - Pretsēņu medikamentie.g. ketoconazols
  - Holestiramīns
  - PSI
- Granulomatozas slimības
  - Sarkoidoze
  - Tuberkuloze
  - Histoplazmoze
  - Kokcidomikoze
- Dažas limfomas

Endocrine Society Clinical Practice Guideline; Journal of Clinical Endocrinology & Metabolism; 2011; 96(7) 1911–1930

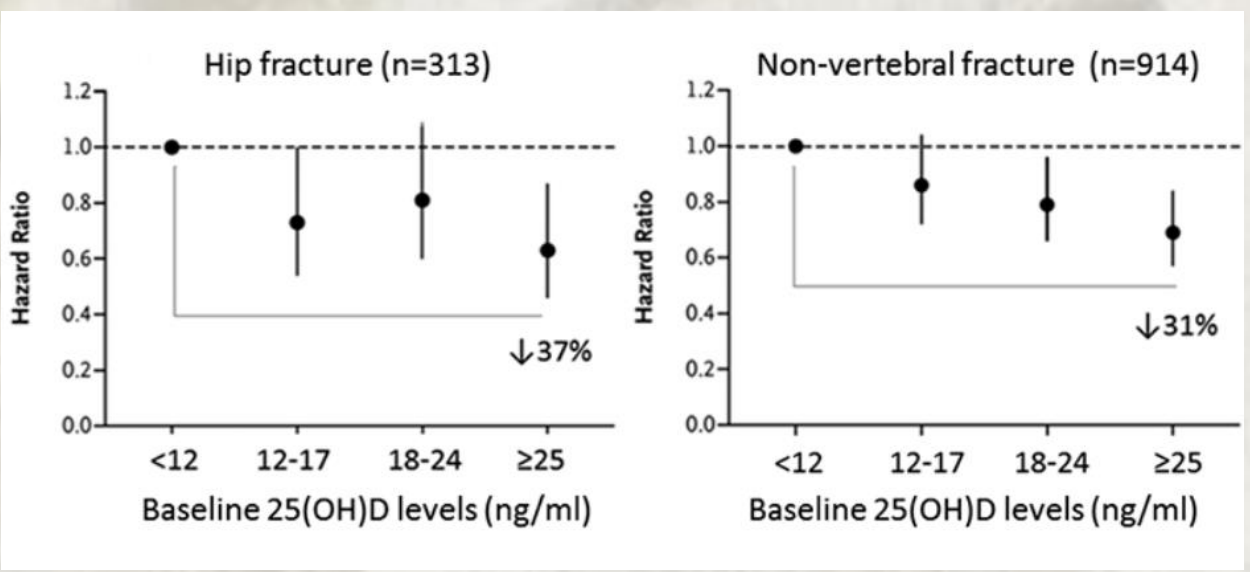
D vitamīna deficīta riska grupas

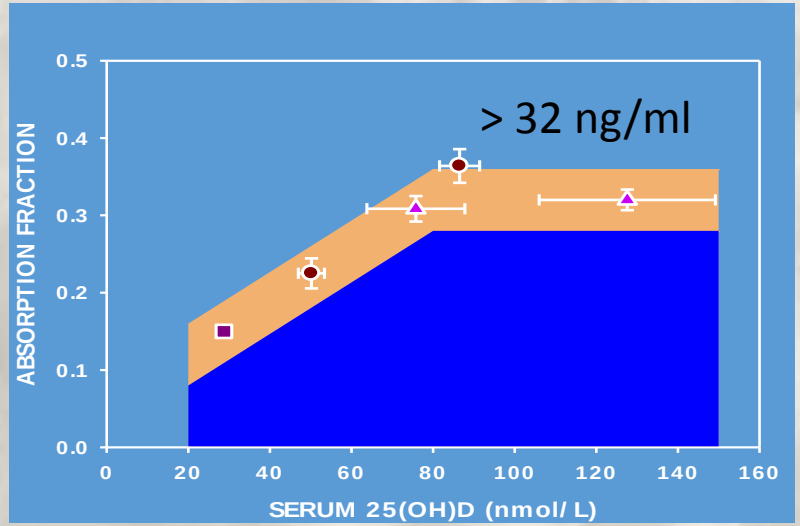
Slimības	
Balsta-kustību sistēma	Rahīts, osteomalācija, osteoporoze, kaulu sāpes, kaulu deformācijas, stājas defekti, nelielas traumas lūzumi, osteonekroze
CA/P vielmaiņas traucējumi	Izmaiņas kalcēmijā, kalciūrijā, fosfatēmijā, fosfatūrijā
Ilgstoši lietoti medikamenti	GKS, ketakonazols, pretepilepsijas med, antiretrovirālie med.
Malabsorbcijas stāvokļi	Malabsorbcijas stāvokļi, cistiskā fibroze, iekaisīgas zarnu kaites
Aknu slimības	Aknu mazspēja, holestāze, nealkohola taukainā hepatoze
Nieru slimības	Nieru mazspēja, nefrokalcinoze, pēc nieres transplantācijas
Endokrīnās slimības	Hiper- un hipoparatireoze, hiper- un hipotireoze, cukura diabēts, augšanas hormona deficīts, anorexia nervosa, autoimūns poliglandulārs sindroms
Somatiskās attīstības trauc.	Īss augums, ļoti garš augums, adipozitāte, kaheksija
Neiroloģiskas slimības	Cerebrāla trieka, hroniska imobilizācija, autisms, multiplā skleroze, epilepsija, miopātijas
Alerģijas	Astma, atopisks dermatīts
Autoimūnas slimības	Kolagenozes, AR, ādas autoimīnās slimības, citas ..
Imunitātes defekti	Biežas elpceļu infekcijas, citas hroniskas un recidivējošas infekcijas
Audzēji	Asinsrades audzēji, solīdo orgānu audzēji
Kardiovaskulārās slimības	Arteriāla hipertensija, KSS

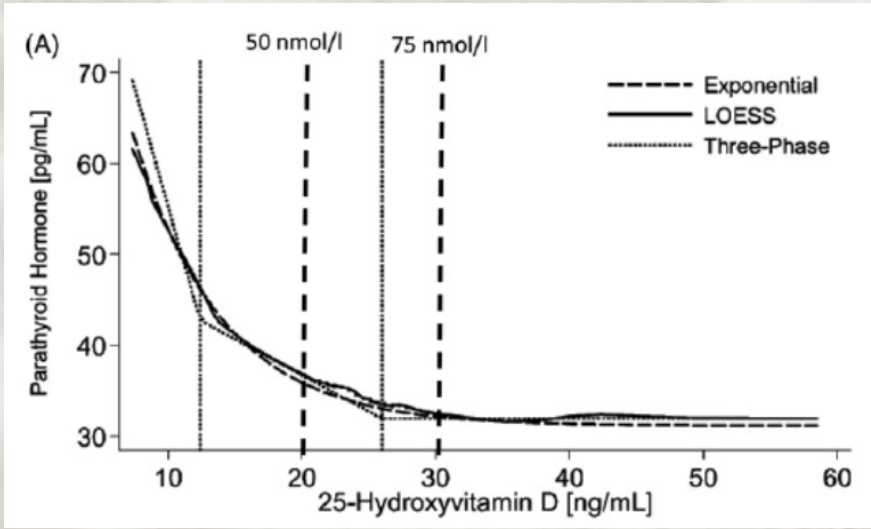
Vitamin D Supplementation Guidelines for General Population and Groups at Risk of Vitamin D Deficiency in Poland, 2018

Kādam jābūt D vitamīna līmenim?

- Kritēriji optimālam D vitamīna līmenim
  - D vitamīns un Ca++ uzsūkšanās
  - D vitamīns un PTH līmenis
  - D vitamīns un lūzumu risks

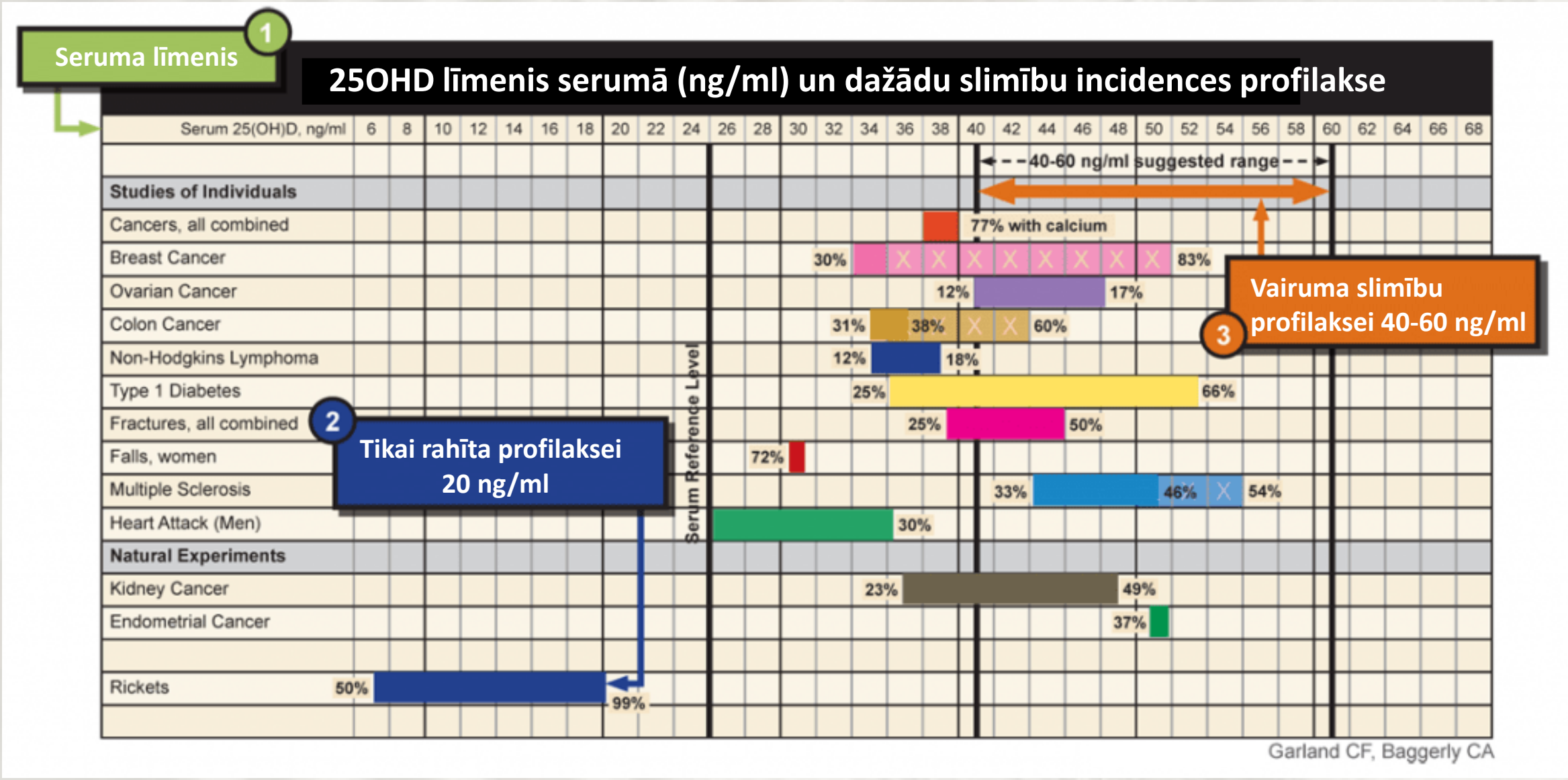






Heaney RP . Am J Clin Nutr 2008;88:541S-544S
Rizzoli R et al.Current Medical Research & Opinion Vol. 29, No. 4, 2013, 305–313
Bischoff-Ferrari HA, et al. N Engl J Med. 2012;367:40–9.

Kādam jābūt D vitamīna līmenim?



Kādam jābūt D vitamīna līmenim?

25OH D vitamīna līmenis (ng/ml) – dažādu organizāciju ieteikumi						
	Vitamin D Council/Vitamin D Society	Endocrine Society 2011	LOKMSA Vadlīnijas 2012	NOS 2018	Polijas D vitamīna vadlīnijas 2018	D vitamīna eksperti 2019
Deficīts	0-30	0-20	0-20	0-10	0-20	0-12
Nepietiekamība	31-39	21-29	21-29	10-20	20-30	12-20
Pietiekams/ Optimāls	40-(60)80	>30/40-60	30-60	> 20/	30-50	20(30)-50
Toksicitāte	> 150	> 100	> 150		> 100	> 100

Bouillon R, et al. Endocr Rev, 2019;40:1109-1151
Giustina A, et al. J Clin Endocrinol Metab, 2019;104:234-240
Dawson-Hughes B. Vitamin D deficiency in adults. UpToDate.com; 2019

Kā nozīmēt D vitamīna terapiju?

- Kas to dara?
- Orāli vai parenterāli?
- Ikdienas režīmā vai intermitējoši?
- Ar kādu devu uzsākt ārstēšanu?
- Kā turpināt?

Kas nozīmē D vitamīna terapiju?

- Parasti D vitamīna terapiju nozīmē ārsts, kurš pirmais saskaras ar iespējamo D vitamīna deficīta problēmu konkrētajam pacientam (ģimenes ārsts, endokrinologs, reimatologs, traumatologs, neirologs u.c.)
- Kad jāmeklē speciālista (endokrinologa, osteoporozes speciālista, nefrologa, u.c.) palīdzība? Ja pacientam ir:
  - Zināma hiperparatireoze, hipertireoze
  - Zināma hiperkalcēmija (meklējot granulomatozas slimības – sarkoidozi, tuberkulozi u.c. vai limfomu) vai hiperkalciūrija
  - Aizdomas par "ģenētisku" rahītu bērnībā
  - Aizdomas par audzēja izraisītu skeleta bojājumu
  - Malabsorbcijas sindromi
  - Nieru slimības ar HNS
    - HNS 4 un 5 parasti kombinē natīvo D3 un aktīvo D3 vitamīnu
  - Nierakmeņu slimība vai nefrokalcinoze

Orāla vai intramuskulāra D vitamīna terapija?

- Perorāla lietošana – galvenais D vitamīna ievades veids
- Lai gan i/m ievade nodrošina 100% līdzestību, tomēr ir faktori, kas neļauj to izvēlēties kā galveno ievades ceļu:
  - Mazāk paredzama biopieejamība –būtiska interindividuāla uzsūkšanās variabilitāte
  - Lēnāks D vitamīna līmeņa pieaugums

Romagnoli E, et al. J Clin Endocrinol Metab. 2008;93(8):3015-3020.

Nugent C, et al. Ir J Med Sci. 2010;179(1):57-61.

Ikdienas vai intermitējoša D vitamīna terapija?

- Reizi dienā, nedēļā vai mēnesī nozīmētas D vitamīna devas vienādā mērā paaugstina 25(OH)D vitamīna līmeni serumā
- Retāki D vitamīna ievades režīmi, piemēram, vienreizējas lielas devas (300.000 SV vai augstākas) pusgadā vai gadā agrāk tika ievadītas pacientiem, kuriem bija līdzestības problēmas, lietojot mazas devas bieži. Tomēr pēdējo gadu pētījumi liecina, ka lielas intermitējošas D vitamīna devas nav efektīvas vai pat var palielināt lūzumu risku
  - D vitamīna deva 500,000 SV reizi gadā 3-5 gadu garumā 2256 sievietēm pēc 70 gadu vecuma palielināja lūzumu risku RR 1.15 (95% CI1.02–1.30; *P* = 0.03) un kritienu risku RR 1.26 (95% CI1.00–1.59; *P* = 0.47)

Ish-Shalom S, et al. *Clin Endocrinol Metab*. 2008;93(9):3430-3435.
Smith H, et al. *Rheumatology*. 2007;46(12):1852-1857.
Sanders KM, et al. *JAMA*. 2010;303(18):1815-1822.

Ar kādu devu uzsākt D vitamīna terapiju?

- D vitamīna terapijas uzsākšanas veidi:
  - **Devas titrēšanas taktika**
  - Fiksētas devas taktika
- **Devas titrēšana** - gadījumos, kad D vitamīna deficīta korekcijai jābūt ātrai (pacienti ar simptomātisku slimību, pacienti ar smagu osteoporozi, kuriem jāsāk terapija ar potentu antiresorbtīvu vai anabolu preparātu), **ārstēšanu uzsāk ar augstāku "piesātinošu" devu un, sasniedzot vēlamo 25(OH)D līmeni, devu samazina un turpina uzturošo terapiju**. Priekšrocības:
  - 25(OH)D līmeni nosaka ne vien ārējie faktori (insolācija, diēta), bet arī pacientu īpatnības – ģenētiskie faktori, ķermeņa uzbūve, D vitamīna biopieejamība. Visu to ņem vērā, titrējot D vitamīna devu
- Gadījumos, kad D vitamīna deficīta korekcija nav tik steidzama un izejas D vitamīna līmenis ir diezgan tuvu vēlamajam, terapiju var sākt ar uzturošo devu

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National Osteoporosis Society

TREAT

HOW TO TREAT VITAMIN D DEFICIENCY

Rapid correction if:

- Symptoms of vitamin D deficiency
- About to start treatment with potent antiresorptive agent (zoledronate or denosumab or teriparatide)

- **Approximately** 300,000 IU vitamin D_3 (or D_2) orally in divided doses over 6-10 weeks
- Commence maintenance vitamin D 4 weeks after loading as per elective correction*

***Elective correction** in all other instances

- When co-prescribing vitamin D supplements with an oral antiresorptive agent, maintenance therapy may be started without the use of loading doses.

- 800-2,000 IU vitamin D_3 daily or intermittently at higher equivalent dose

FOLLOW UP

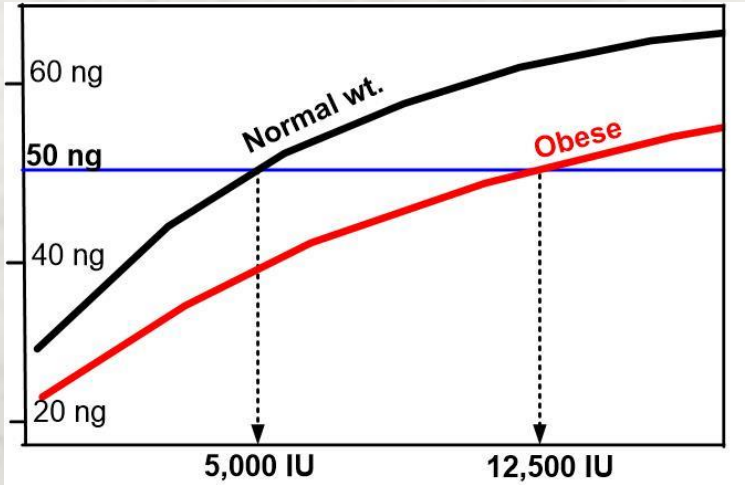
CAUTION

- Check serum adjusted calcium one month after treating with loading doses of vitamin D. Vitamin D repletion may unmask primary hyperparathyroidism

- Routine repeat vitamin D testing is generally unnecessary

Cik liela būs D vitamīna deva?

- Aptuvena D vitamīna devas/D vitamīna līmeņa attiecība: **pievienojot terapijā 100 SV D vitamīna dienā, 25(OH)D koncentrācija serumā palielināsies par 1-2 ng/mL** (ar ļoti lielu variabilitāti dažādos literatūras avotos)
- D vitamīna devas/D vitamīna līmeņa attiecības līkne nav lineāra – tā paliek lēzenāka pie augstākām 25(OH)D koncentrācijām
- 25(OH)D līmeņa kāpums ir
  - Ievērojami augstāks indivīdiem ar zemāku izejas 25(OH)D līmeni
  - Zemāks indivīdiem ar augstāku ĶMI



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CIK ILGI PACIENTAM JĀLIETO
PA 5000 SV/DIENĀ?

Sasniedzot optimālo 25(OH)D vitamīna līmeni (>45 ng/ml), jāturpina lietot uzturošā holekalciferola jeb D_3 vitamīna deva

SVARS / 25(OH)D vitamīns	50–59 kg	60–69 kg	70–79 kg	80–89 kg	90–99 kg	100–109 kg	110–119 kg	120–129 kg
5–9 ng/ml	50–66 dienas	60–77 dienas	70–89 dienas	80–99 dienas	90–111 dienas	101–122 dienas	111–133 dienas	121–145 dienas
10–19 ng/ml	36–58 dienas	43–67 dienas	51–77 dienas	58–87 dienas	66–97 dienas	73–107 dienas	80–116 dienas	87–126 dienas
20–29 ng/ml	22–41 dienas	27–48 dienas	31–55 dienas	36–62 dienas	40–69 dienas	45–76 dienas	49–83 dienas	53–90 dienas
30–39 ng/ml	8–25 dienas	10–29 dienas	12–33 dienas	14–37 dienas	15–42 dienas	17–46 dienas	19–50 dienas	20–54 dienas

VITAMIN D SUPPLEMENTATION IN GENERAL POPULATION, IN GROUPS AT RISK OF VITAMIN D DEFICIENCY AND IN PERSONS WITH LABORATORY CONFIRMED VITAMIN D DEFICIENCY – a practical guidelines for prophylactics and therapetic procedures in Poland

Vitamin D supplementation in general population and in groups at risk of vitamin D deficiency

Pregnancy and lactation

1) Women planning pregnancy should receive adequate vitamin D supply, the same as in the general adult population, if it is possible under the control of 25(OH)D concentration (1⊕⊕⊕);
2) When pregnancy is confirmed, supplementation should be carried out under the control of 25(OH)D concentration, to maintain optimal concentrations within ranges of >30-50 ng/ml (1⊕⊕⊕);
3) If the assessment of 25(OH)D concentration is not possible, it is recommended to use vitamin D at a dose of **2000 IU/day**, throughout pregnancy and lactation (1⊕⊕⊕);

Preterm neonates
≤ 32 weeks of gestation

1)) It is recommended to start supplementation at a dose of **800 IU/day** from the first days of life (if enteral nutrition is possible), regardless the way of feeding (1⊕⊕⊕);
2) Supplementation should be carried out under the control of 25(OH)D concentration, both during hospitalization (the first control after 4 weeks of supplementation), as well as in the out-patient care (1⊕⊕);
3) When achieving a total dose of 1000 IU/day, combining supplements and diet, there is a risk of vitamin D overdose, particularly in neonates with birth weight <1000 g (1⊕⊕⊕);

Preterm neonates
born at 33-36 weeks of gestation

1) **400 IU/day** from the first days of life, regardless the way of feeding (1⊕⊕⊕);
2) There is no need to assay 25(OH)D concentrations routinely (1⊕⊕⊕);
3) Supplementation carried out under the control of 25(OH)D concentration should be considered in children in the risk groups (parenteral nutrition >2 weeks, ketoconazole >2 weeks, anticonvulsant treatment, cholestasis, birth weight <1500 g) (2⊕⊕);

Neonates and infants

1) 0-6 months:
400 IU/day from first days of life, regardless the way of feeding (1⊕⊕⊕);
2) 6-12 months:
400-600 IU/day, depending on daily amount of vitamin D taken with food (1⊕⊕⊕);

1 µg = 40 IU

Upper tolerable limits (UL) for general healthy population :
1) Neonates and infants – 1000 IU/d
2) Children 1-10 yrs – 2000 IU/d
3) Adolescents 11-18 yrs – 4000 IU/d
4) Adults and seniors – 4000 IU/d
Upper tolerable limits should not be confused with recommended doses during well-controlled treatment of vitamin D deficiency and should not be exceeded without medical supervision (1⊕⊕⊕)

Children 1-10 yrs

1) In the period from May to September, if guidelines for insolation are met, supplementation is not necessary, although still recommended and safe (1⊕⊕⊕);
2) If insolation guidelines are not fulfilled, supplementation of **600-1000 IU/day** is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1⊕⊕⊕);
3) Obese children require **1200-2000 IU/day**, depending on severity of obesity (1⊕⊕⊕);

Adolescents 11-18 yrs

1) In the period from May to September, if guidelines for insolation are met, supplementation is not necessary, although still recommended and safe (1⊕⊕⊕);
2) If insolation guidelines are not fulfilled, supplementation of **800-2000 IU/day** is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1⊕⊕⊕);
3) Obese adolescents require **1600-4000 IU/day**, depending on severity of obesity (1⊕⊕⊕);

Adults 19-65 yrs

1) In the period from May to September, if guidelines for insolation are met, supplementation is not necessary, although still recommended and safe (1⊕⊕⊕);
2) If insolation guidelines are not fulfilled, supplementation of **800-2000 IU/day** is recommended, based on body weight and the dietary vitamin D intake, throughout a year (1⊕⊕⊕);
3) Obese adults require **1600-4000 IU/day**, depending on severity of obesity (1⊕⊕⊕);

Seniors > 65-75 yrs

1) Due to decreased efficacy of the skin synthesis, supplementation of vitamin D in the dose of **800-2000 IU/day**, based on body weight and the dietary vitamin D intake is recommended throughout a year (1⊕⊕⊕);
2) Obese seniors require **1600-4000 IU/day**, depending on severity of obesity (1⊕⊕⊕);

Seniors >75 yrs

1) Due to decreased efficacy of the skin synthesis, potential malabsorption and altered metabolism of vitamin D, supplementation of **2000-4000 IU/day**, based on body weight and the dietary vitamin D intake is recommended throughout a year (2⊕⊕);
2) Obese eldest seniors require **4000-8000 IU/day**, depending on severity of obesity (2⊕⊕);

Supplementation in groups at risk of vitamin D hypersensitivity

1) Prior to initiating the supplementation, the probability of vitamin D hypersensitivity should be assessed if feasible (hypercalcemia, hypercalciuria, nephrocalcinosis, nephrolithiasis, *CYP24A1* gene mutation, *SLC34A1* gene mutation or history of other types of vitamin D hypersensitivity in an individual or family members). This recommendation applies to all age groups as well as to groups at the risk of vitamin D deficiency (1⊕⊕⊕);
2) In groups at the risk of vitamin D hypersensitivity, supplementation should be supervised and carried out carefully and in an individual manner, preferably under the control of calcium-phosphate parameters, particularly calcemia, calciuria, PTH, 25(OH)D and $1,25(OH)_2D$ (1⊕⊕);

Vitamin D supplementation and treatment regimes in relation to 25(OH)D concentration

Severe Deficiency 0-10 ng/ml (1⊕⊕⊕);

1) Therapy in relation to age and body weight; control assay of 25(OH)D concentration should be performed after 1 to 3 months of therapy (1⊕⊕⊕);
2) Recommended therapeutic doses:
- **0-12 months of age: 2000 IU/day (1⊕⊕⊕);**
- **1-10 years: 3000-6000 IU/day (1⊕⊕⊕);**
- **>10 years: 6000 IU/day (1⊕⊕⊕);**

3) Treatment should be carried out for 3 months or until the 25(OH)D concentration of >30-50 ng/ml is reached, then it is recommended to use consecutive maintenance dose i.e. a prophylactic dose recommended for general population, in relation to age and body weight (1⊕⊕⊕);
4) In patients with skeletal symptoms and bone mineral disorders (bone deformations, bone pain, history of fragility fractures), it is necessary to assess and monitor parameters of calcium-phosphate metabolism (Ca, PO_4, ALPL, PTH, Ca/creatinine ratio in urine), and, if available – to examine bone mineral density using DXA (2⊕⊕);

Deficiency >10-20 ng/ml (1⊕⊕⊕);

1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2⊕⊕);
2) If vitamin D supplementation was appropriate, it is recommended to increase the dose by 100% and to assess 25(OH)D concentration in 3 months' time (2⊕⊕);
3) If vitamin D was not supplemented previously, it is recommended to start vitamin D intake at maximal doses recommended for peers from the general population and to assess 25(OH)D concentration in 3 months' time (2⊕⊕);
4) In patients with skeletal symptoms (bone deformations, bone pain, history of fragility fractures), it is indicated to assess calcium-phosphate metabolism (Ca, PO_4, ALPL, PTH, Ca/creatinine ratio in urine), and, if available – bone mineral density using DXA (2⊕⊕);

Suboptimal >20-30 ng/ml (1⊕⊕⊕);

1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2⊕⊕);
2) If vitamin D supplementation was appropriate, it is recommended to increase the dose by 50% and to consider the assessment of 25(OH)D concentration in 6 months' time (2⊕⊕);
3) If vitamin D was not supplemented previously, it is recommended to start vitamin D intake at doses recommended for peers from the general population (2⊕⊕);

1 ng/mL = 2.5 nmol/L

Optimal >30-50 ng/ml (1⊕⊕⊕);

1) Continue previous management (1⊕⊕⊕);

General recommendations
Prophylactic dosing of vitamin D in the general population should be individualized depending on age, body weight, insolation (season, time of year), sun exposure of an individual, dietary habits and lifestyle (1⊕⊕). Prophylactic dosing of vitamin D in the risk groups of vitamin D deficiency should be implemented according to arrangements for the general population. If no specific practice guidelines are established, the maximal admissible doses for a given age group in the general population are recommended for use in the risk groups of vitamin D deficiency (2⊕⊕). In the general population, in case of vitamin D deficiency ascertained by laboratory assays, the administration of vitamin D should be based on doses dependent on serum 25(OH)D concentration and chronological (calendar) age, in relation to body weight (2⊕⊕). In the risk groups, the dosing of vitamin D in case of vitamin D deficiency ascertained by laboratory assays, should be based on doses dependent on the 25(OH)D concentration and age, with regard to the nature of the disease, medical therapy, and body weight (1⊕⊕). In the general population, the specific indications for 25(OH)D assay testing are not established and 25(OH)D concentration screening is not recommended (1⊕⊕). In the risk groups, the evaluation of vitamin D status, based on 25(OH)D concentration assay, is recommended (1⊕⊕).

High >50-75 ng/ml (2⊕⊕);

1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2⊕⊕);
2) If vitamin D supplementation was appropriate, it is recommended to reduce the dose by 50%, and to consider assessment of 25(OH)D concentration within the consecutive 3 month-period (2⊕⊕);
3) If vitamin D was supplemented at doses higher than recommended, the vitamin D supply should be ceased for 1 month, and then doses recommended for peers from the general population should be started (2⊕⊕);

High >75-100 ng/ml (2⊕⊕);

1) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2⊕⊕);
2) Vitamin D intake should be suspended for 1-2 months (2⊕⊕);
3) In neonates, infants and toddlers, calcemia and calciuria should be assessed, vitamin D hypersensitivity should be excluded and the control assay of 25(OH)D concentration should be carried out (2⊕⊕);
4) There is a possibility to re-entry vitamin D supplementation at minimal doses recommended for peers from the general population, after 1-2 months or, in case of neonates, infants and toddlers after reaching 25(OH)D concentrations ≤50 ng/ml (2⊕⊕);

Toxic >100 ng/ml (1⊕⊕⊕)

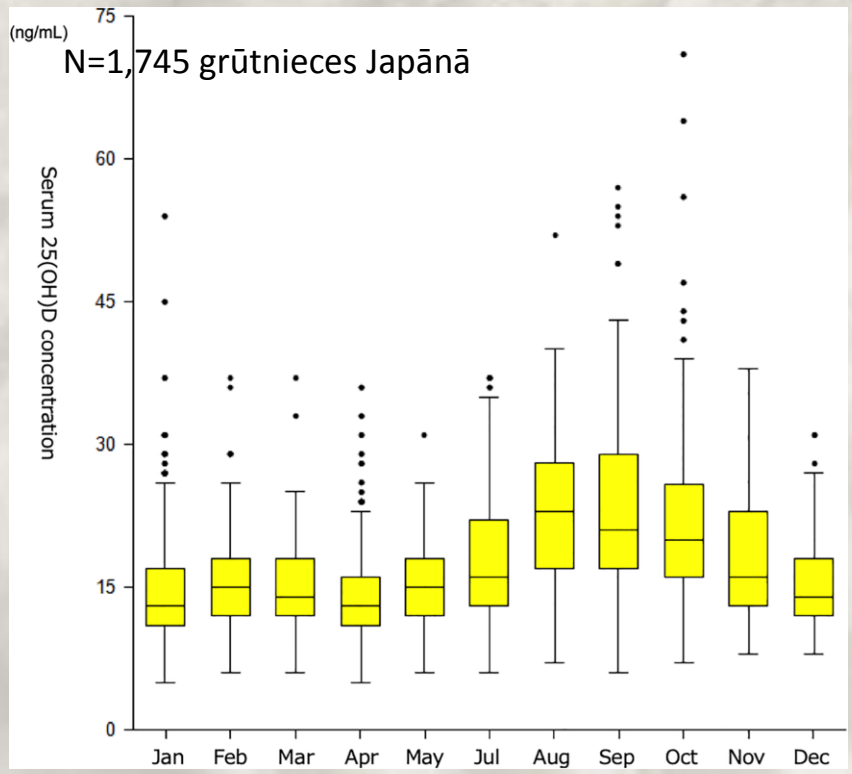
1) Vitamin D supplementation has to be absolutely terminated; calcemia and calciuria should be assessed, and 25(OH)D concentration should be monitored at 1-month intervals until 25(OH)D concentrations of ≤50 ng/ml are reached (1⊕⊕⊕);
2) Vitamin D intoxication is defined as the state in which the 25(OH)D concentration >100 ng/ml is accompanied by hypercalcemia, hypercalciuria and apparent PTH suppression (1⊕⊕⊕);
3) In case of clinical symptoms of vitamin D intoxication, a treatment should be immediately initiated (1⊕⊕⊕);
4) Verify if previously used supplementation was appropriate, and correct the management accordingly (regularity of intake, dosing, type of preparation, the way of supply) (2⊕⊕);
5) There is a possibility to re-entry vitamin D supplementation at doses recommended for peers from the general population, after reaching normocalcemia, normocalciuria and 25(OH)D concentrations ≤50 ng/ml, followed by excluding vitamin D hypersensitivity (2⊕⊕);

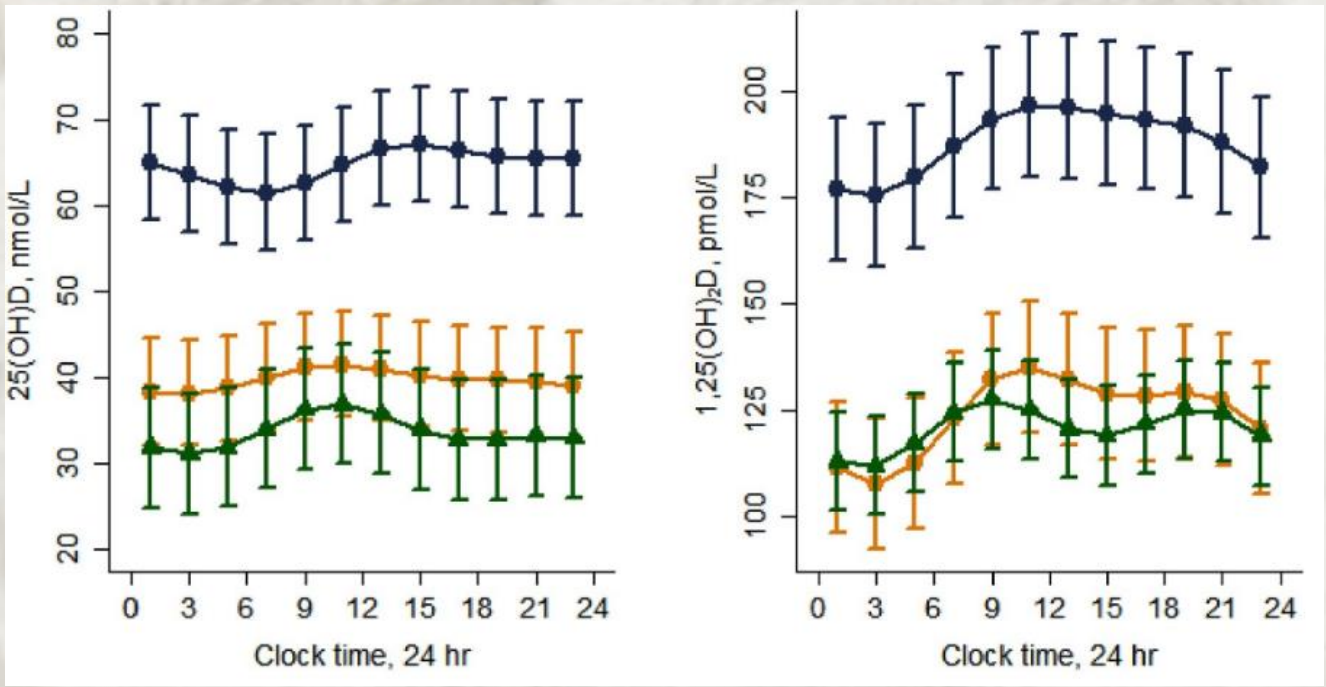
GRADE: 1 – strong recommendation (application in the general population and in all patients in most circumstances, benefits clearly overweigh the risks) and 2 – weak recommendation (consensus opinion of working group or to be considered; the best action may depend on circumstances, benefits and risk closely balanced or uncertain). Quality of evidence was assigned as follows: ⊕⊕⊕ high-quality (prospective cohort or RCT studies, at low risk of bias); ⊕⊕ moderate quality (observational or clinical trials with methodological flaws, inconsistent or indirect evidences); ⊕ low quality (case reports, case series or non-systematic clinical observations).

Front. Endocrinol., 31 May 2018

Kā kontrolēt D vitamīna līmeni?

- 1 mēnesi pēc terapijas uzsākšanas ar "piesātinošo devu", kontrolēt Ca++ serumā (normalizējoties D līmenim, var izpausties PHPT)
- 25(OH)D līmeni kontrolēt ne ātrāk kā **12** nedēļas pēc terapijas uzsākšanas
- Pēc tam vismaz 1 x ziemā un vasarā – rezultāts būs reprezentatīvs konkrētajam cilvēkam arī turpmāk (ja nepievienojas citi veselības traucējumi, kas var ietekmēt 25(OH)D līmeni)
- Atkārtota 25(OH)D līmeņa kontrole vajadzīga pirms kārtējās potentu antiresorbtīvo preparātu (ZOL, DEN) ievades
- Kontrolēt tajā paša laboratorijā, ja iespējams, tajā pašā dienas laikā





PLOS ONE | https://doi.org/10.1371/journal.pone.0214797 April 10, 2019
Jones KS, et al. J Steroid Biochem Mol Biol. 2017 Sep;172:130-135

National Osteoporosis Society

Vitamin D and Bone Health:

A Practical Clinical Guideline for Patient Management

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Publication date: December 2018

Latvijā joprojām nav, taču ir ļoti vajadzīgas savas D vitamīna vadlīnijas …

Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

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J Clin Endocrinol Metab, July 2011, 96(7):1911–1930

Vitamin D Supplementation Guidelines for General Population and Groups at Risk of Vitamin D Deficiency in Poland—Recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel With Participation of National Specialist Consultants and Representatives of Scientific Societies—2018 Update

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