vitamin Defense in ENT

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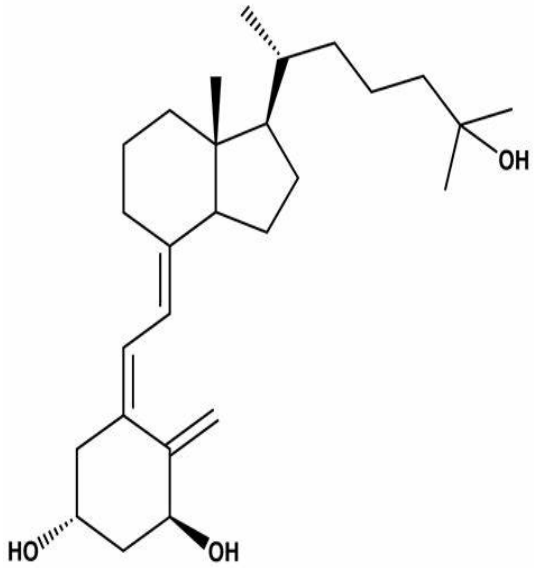
Learning Outcomes

- Review vitamin D function, values, and sources
- Examine the impact of vitamin D deficiency in ENT disorders

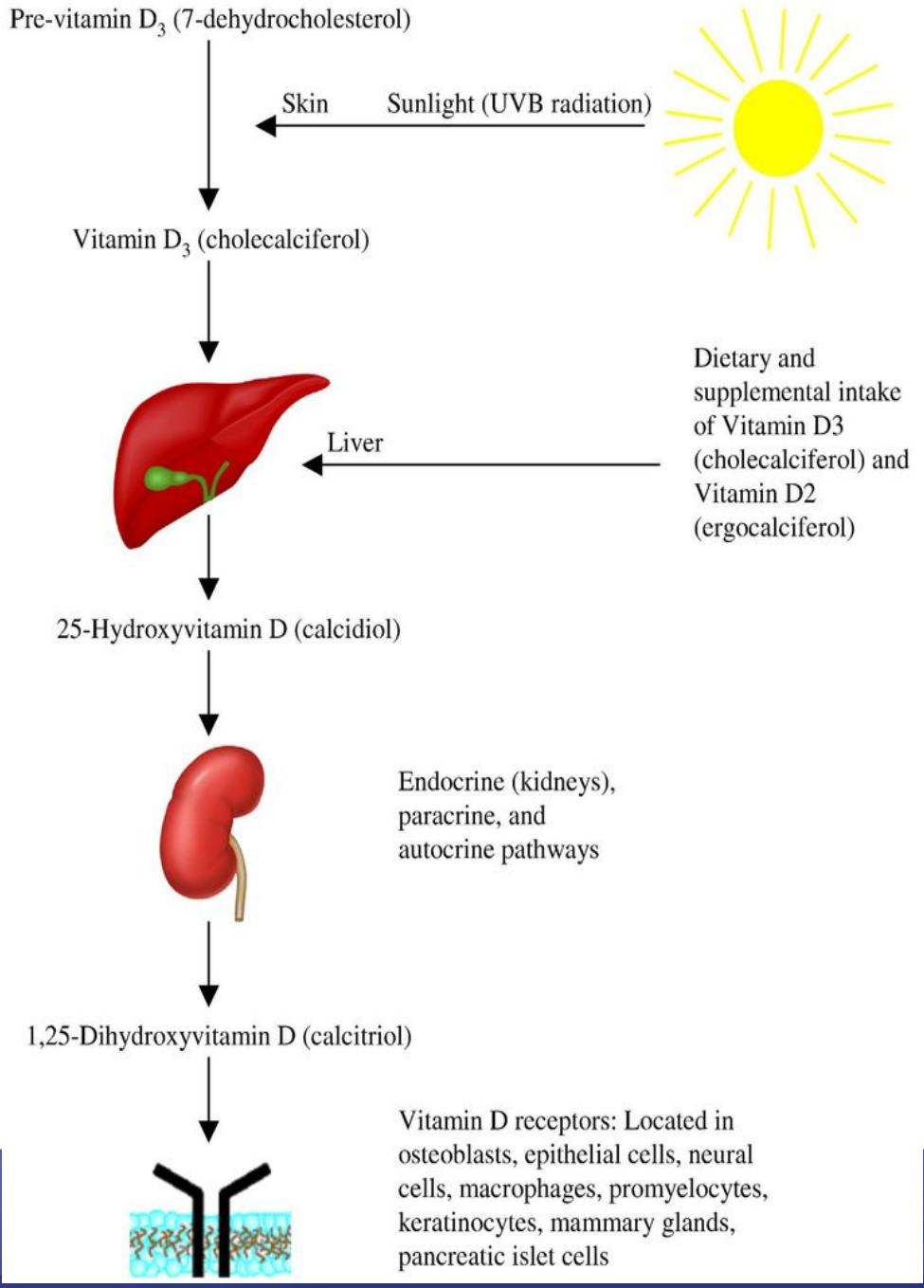
Vitamin D

- Member of steroid nuclear hormone family – secosteroid
- Essential nutrient to sustain health
- 2 categories of physiological effects
  - Skeletal: calcium and magnesium metabolism
  - Non-Skeletal: immune functions, inflammation, anti-oxidation, antifibrosis, inhibitory effects of many kinds of malignancies
- 5 forms of vitamin D – 2 dominant
  - D3=cholecalciferol
  - D2=ergocalciferol



Biosynthesized or absorbed through dietary ingestion

Source	Vitamin D Content
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D_3
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D_3 or D_2
Canned (3.5 oz)	About 300–600 IU of vitamin D_3
Sardines, canned (3.5 oz)	About 300 IU of vitamin D_3
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D_3
Tuna, canned (3.6 oz)	About 230 IU of vitamin D_3
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D_3
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D_2
Sun-dried (3.5 oz)	About 1600 IU of vitamin D_2
Egg yolk	About 20 IU of vitamin D_3 or D_2
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose)†	About 3000 IU of vitamin D_3
Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D_3
Fortified orange juice	About 100 IU/8 oz vitamin D_3
Infant formulas	About 100 IU/8 oz vitamin D_3
Fortified yogurts	About 100 IU/8 oz, usually vitamin D_3
Fortified butter	About 50 IU/3.5 oz, usually vitamin D_3
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	About 100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D_3



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Vitamin D levels

- Many different methods and criteria
  - National Academy of Medicine (IOM)
    - Sufficient = 20-40 ng/ml
  - National Osteoporosis Foundation
  - International Osteoporosis Foundation
  - American Geriatric Society

  } minimum 30 ng/ml

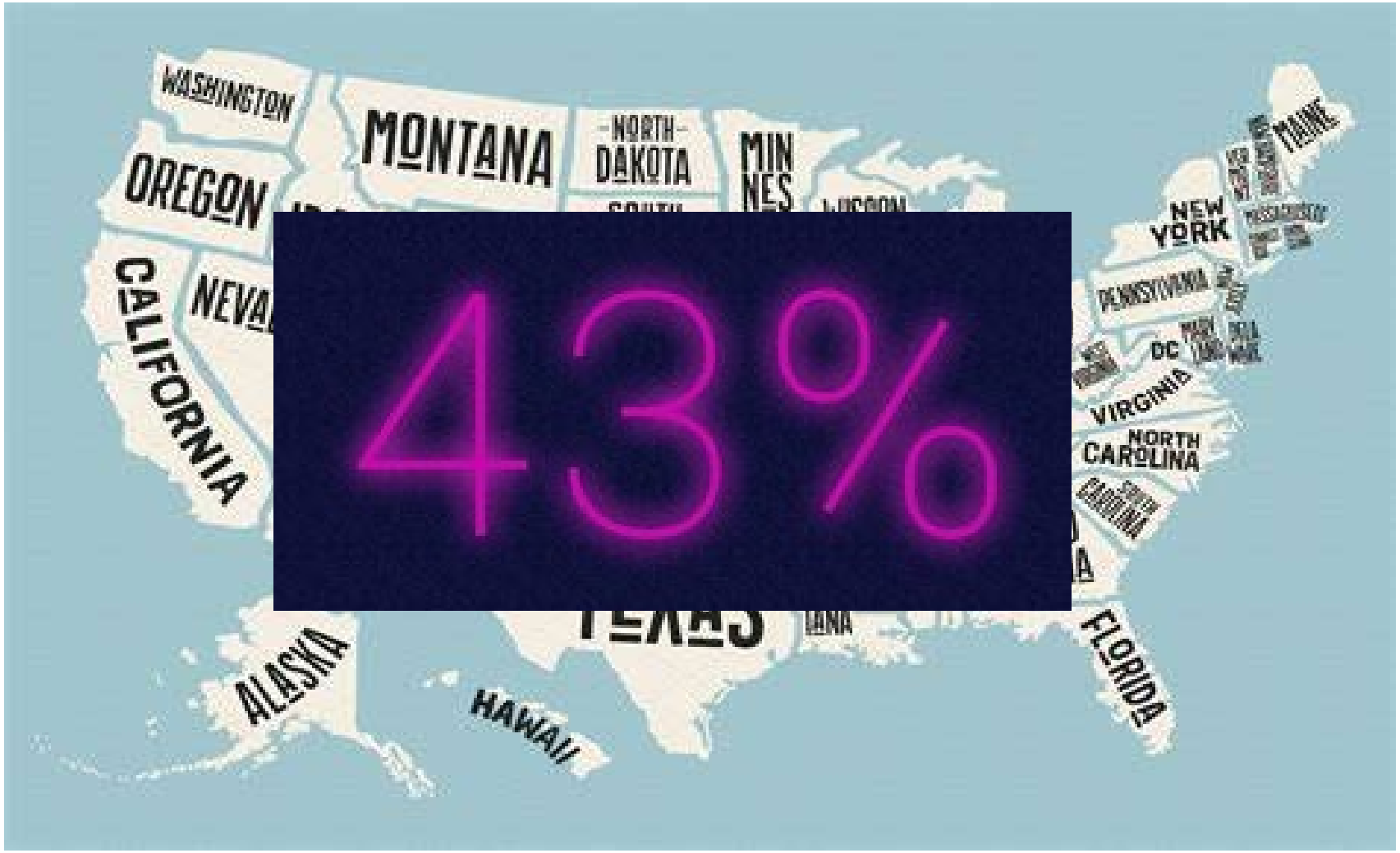
  - Endocrine Society prefers 40-60 ng/ml
- Usually looking at optimal concentration for skeletal health
- Serum 25 hydroxyvitamin D (calcidiol) [25(OH)D]
  - Deficiency = $\leq$ 20 ng/ml
  - Insufficiency = 21-29 ng/ml
  - Sufficient = $\geq$ 30 ng/ml

Vitamin D Toxicity

- Insufficient data to determine safe upper limits

- Risk of toxicity when > 100 ng/ml
  - Signs:
    - Hypercalcuria
    - Hypercalcemia

Vitamin D Deficiency



Deficiency Risk Factors

Fiscaletti, M, Stewart, P, & Munns, CF. (2017). The importance of vitamin D in maternal and child health: a global perspective. *Public Health Reviews, 28*:19.

Table 1 Risk factors for low 25OHD concentrations

Risk factors that limit skin exposure to UVB rays
Latitudes above 40° north
Winter season
Exposure in early morning and evening (before 10 AM, after 4 PM)
Cloud cover and atmospheric pollution
Limited time spent outdoors
Customary dress that conceals large portions of the body
Sunscreen use
Dark skin pigmentation
Older age
Risk factors that limit dietary exposure to vitamin D
Low dietary intake of oily fish and egg yolks
Vegetarian diets
Low/no dietary intake of vitamin D fortified foods
Exclusive breastfeeding in infants
No intake of vitamin D supplements
Other risk factors that alter vitamin D supply or metabolism
Vitamin D status of infant depends on vitamin D status of mother during pregnancy
Low dietary calcium intake
Obesity
Genetic factors that affect vitamin D physiology and requirements
Poor renal function
Liver disease and cholestasis
Chronic disease
Malabsorption (coeliac, inflammatory bowel disease, cystic fibrosis, etc.)

What's better – supplements or sunshine?

- Supplements and sunshine are functionally the same
- Supplements may be preferred to reduce the risk of skin cancer from excess sun exposure

- Sun exposure (≥20 –30 minutes around noon daily) versus oral vitamin D3 (500 IU/d) in 8 week randomized placebo-controlled clinical trial of VDD adults
  - More participants in supplement group (54.2%) achieved 25OHD concentrations ≥ 20ng/ml at week 8 than sun exposure group (12.2%) versus control (4.3%)

(Hee-Kyung Joh et al, 2020. *Clinical Nutrition, 39*: 727-736)

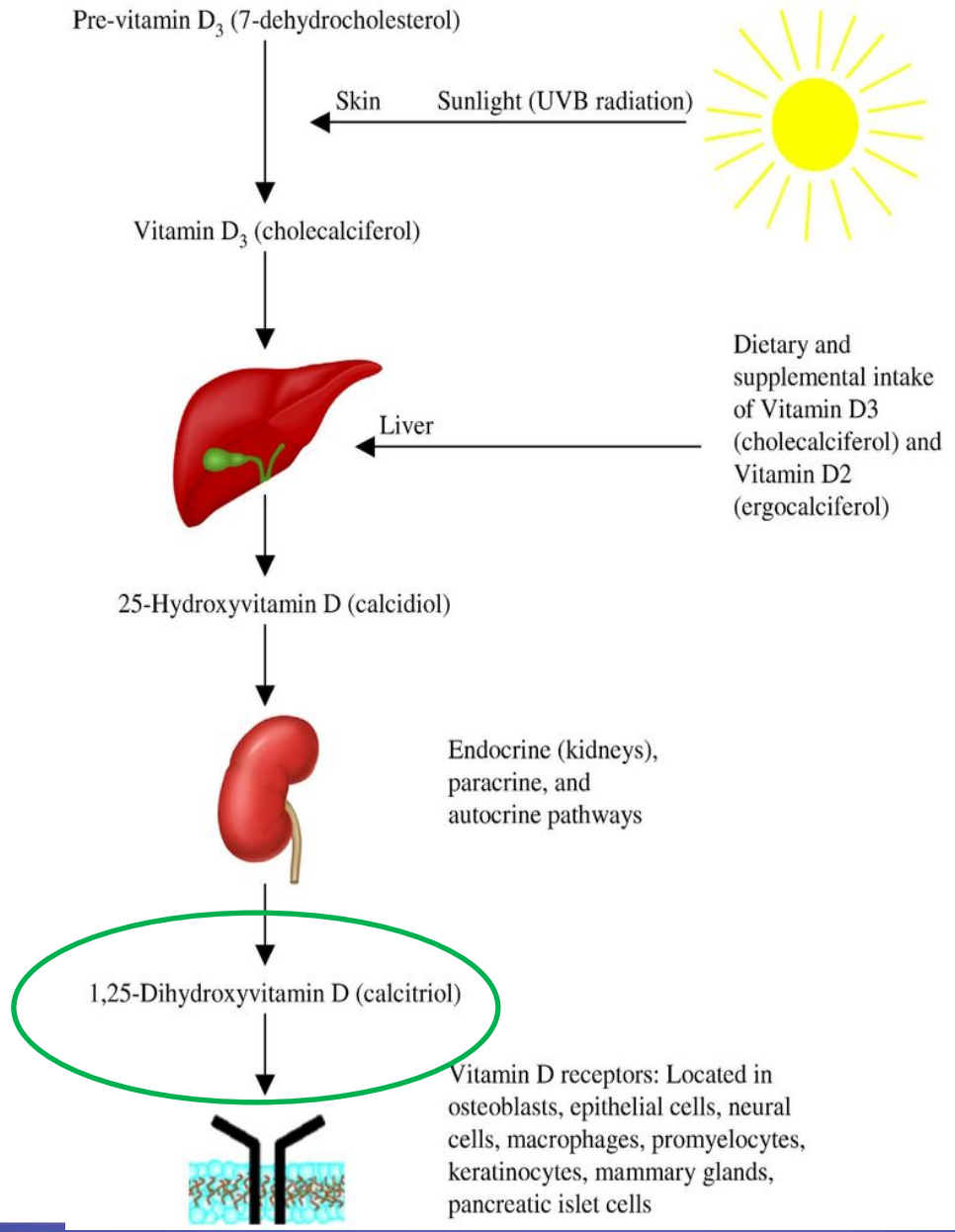
Intake/Supplementation

- D3 (cholecalciferol) recommended over D2 (ergocalciferol)
- Dosing and frequency not well established
- In those with normal absorption:
  - Every 100 units (2.5 mcg) of D3 increases serum 25(OH)D by 0.7 - 1.0 ng/ml
  - Larger increments allowed for those with lower baseline
  - Increments decline when serum 25(OH)D > 40 ng/ml
- For deficient (<12 ng/ml) -- 50,000 iU weekly for 6-8 weeks then 800 iU/d **
- For insufficient (12 – 20 ng/ml) -- 800-1000 iU/d **
- For sufficient (20 – 30 ng/ml) -- 600-800 iU/d for maintenance
  - No follow up after starting supplementation when > 30 ng/ml

**monitor every 3-4 months

Special Group Considerations

- Pregnancy
  - Optimal serum unknown but at least 20 ng/ml
  - NAM recommends 600 iU/d
    - Most prenatal vitamins contain 400 iU
  - ACOG: 1000-2000 iU/d is safe and may be necessary for 25(OH)D > 30 ng/ml
- Malabsorption
  - Individualized supplementation
  - Severe liver disease—may need treatment with vitamin D metabolites
- Chronic Kidney Disease
  - If GFR > 30, then same recommendations as normal renal function
  - If GFR < 30, calcitriol production may be low
    - Concern for secondary hyperparathyroidism
    - Endocrinology involvement



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Dawson-Hughes, B. (2022). Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment. *UpToDate,* Mulder, JE (Ed), UpToDate, Waltham, MA. (Accessed July 6, 2022).

Vitamin D Deficiency & Other Diseases

- Diabetes
  - D combines with receptors on islet Beta cells in pancreas
    - Increases insulin sensitivity
    - Inhibits inflammatory factors
- Cardiovascular Disease
  - Vitamin D receptors in heart and CV system regulate expression of many genes
  - Metabolites act on many parts of CV function
  - Endothelial cells affected
  - Anticoagulant activity
- Cancer
  - <20 ng/ml 25(OH)D associated with 30-50% increases risk of cancers and higher mortality
  - Vitamin D binding protein (VDBP) link

VDBP & Cancer

Disease	VDBP Influence	Mechanism
	Cancers	
Breast cancer	Gc2-2 genotype associated with decreased risk of postmenopausal breast cancer (n = 1402, control: 2608) SNPs: rs17467825, rs2298850 and rs3755967 are associated to the breast cancer risk (n = 818, controls = 935); another study does not support an important role of either calculated circulating free 25(OH)D or circulating VDBP levels in breast cancer risk among predominantly premenopausal women; (controls = 584)	The carcinogenic mechanism is based on the potential to convert Gc to GcMAF, which is a macrophage activator. GcMAF may enhance proapoptotic enzymes activity and induce cell apoptosis via JNK1/2 and p387 pathway—that may inhibit cancer development
Prostate cancer	Decreased risk in of prostate cancer associated with higher serum VDBP levels in men with lower than median 25(OH)D status, where elevated risk in men with higher than median 25(OH)D concentration (n = 950, control = 964); SNP: Rs2282679 in *Gc* has no significant correlation with non-aggressive and aggressive prostate cancer (n = 10,572, controls = 4975)	Extracellular concentrations of VDBP and 25(OH)D result in an upregulation of megalin-mediated internalization of SHBG-bound testosterone
Pancreatic cancer	Higher serum 25(OH)D and serum VDBP are associated with higher pancreatic cancer risk (n = 234, control = 234) among Finnish men population; VDBP or 25(OH)D were not associated with pancreatic cancer (n = 295, two controls n = 590); rs2282679, rs7041 and rs4588 found no significant correlation with pancreas cancer	Reducing free 25(OH)D by VDBP decreases bioavailability; high concentration of VDBP and 25(OH)D could potentially displace 1,25(OH)D with its antitumorigenic properties
Lung cancer	VDBP low serum concentration might be a predictor of subsequent death from non-small cell lung cancer (n = 148 lung cancer patients, 68 patients with other intrathoracic tumors and 33 noncancer controls); GC2-1f combination (TT-CA) has significant and protective association with lung cancer (n = 113, control = 113); Rs7041 in GC gene reduces the risk of Non-Small Cell Lung Cancer risk (n = 446, controls = 425)	Conversion of VDBP to GcMAF may be reduced in malignancy due to the action of α-N-acetylogalactosaminidasa and as a result it might lower macrophage activation
Colorectal cancer	Rs7041 (TG/GG) significant association with colorectal cancers among age 60 years old and older (n = 282, control = 113); Rs4588 (CA/AA) significant association with cancer in males aged 60 years old or less (n = 282, control = 113); Both: Gc/Rs7041 and CYP2R1/rs10741657 polymorphisms decreases the risk of colorectal cancer about 9–12% (n = 920, controls = 1743)	
Basal cell carcinoma	SNP may affect skin carcinogenesis. Among patients with rs7041 and rs4588 233 of them developed BCC and 52.4% among those patients developed multiple BCCs (n = 7983). GC1s homozygotes had lower BCC risk. Rs7041 was associated with BCC development among the youngest group.	SNPs may be associated with BCC development among younger patients
Cutaneous Melanoma	Association between VDBP rs12512631 and risk of cutaneous melanoma among Spanish population (n = 530, controls = 314); No association between VDBP rs1155563 and rs7041 and melanoma risk or prognosis (n = 305, controls = 370)	VDBP variants may influence on vitamin synthesis and distribution

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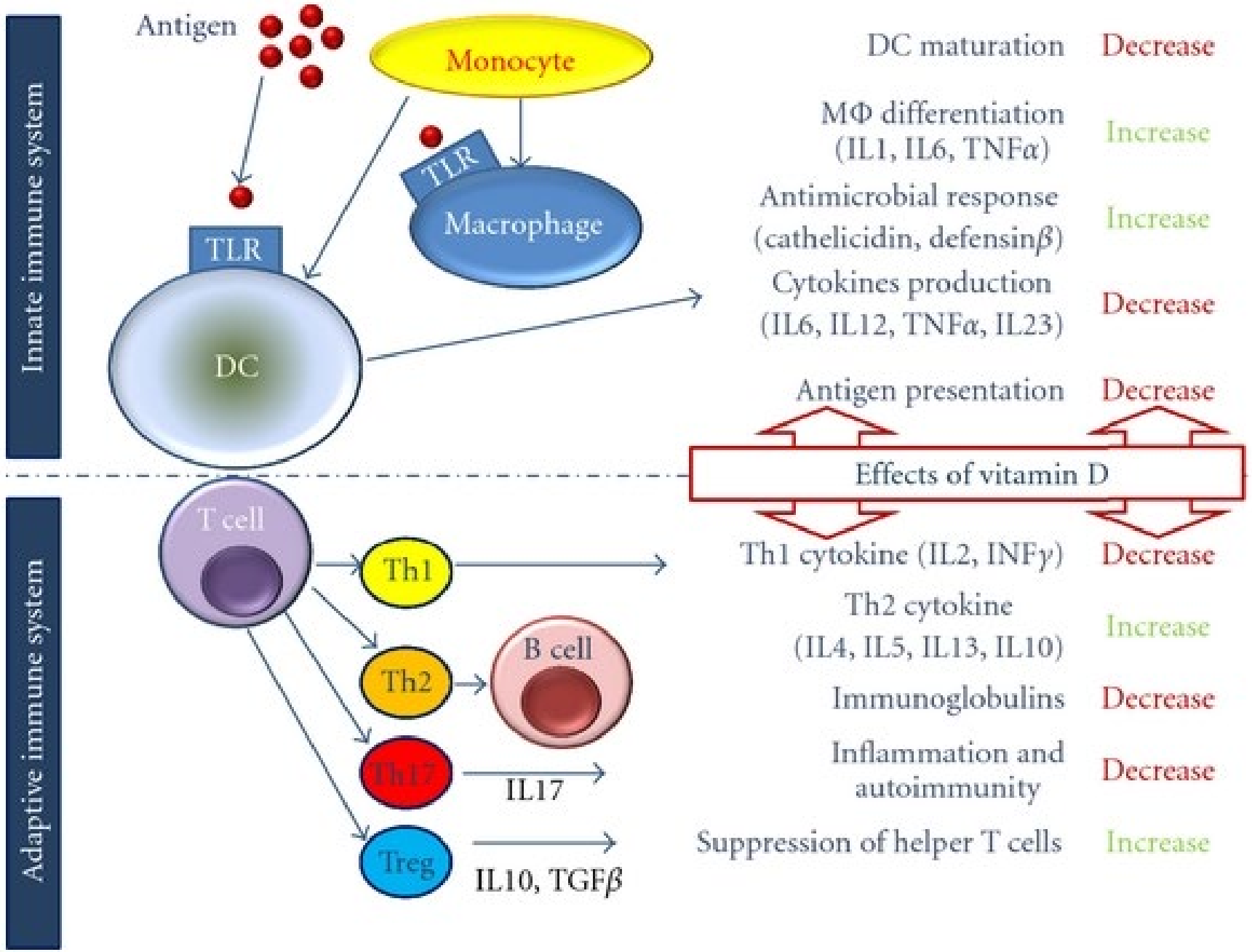
Rozmus, D, Ciesielska, A, Plominski, J, Grzybowski, R, Fiedorowicz, E, Kordulewska, N, Savelkoul, H, Kostyra, E, Cieslinska, A. (2020). Vitamin D binding protein (VDBP) and its gene polymorphisms—The risk of malignant tumors and other diseases. *International Journal of Molecular Sciences, 21,* 7822.

Vitamin D & Immune System

Immunomodulatory activity



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Bacteria Specific Disease

- Vitamin D has direct antimicrobial and antibiofilm activity
  - Klebsiella pneumoniae
  - Escherichia coli
  - Mycobacterium tuberculosis
  - Heliobacter pylori
- Strep specific activity by Vitamin D
  - Enhances neutrophil killing of S. pneumoniae
  - Promotes secretion of antimicrobial peptides
  - Induces anti-inflammatory activity
  - Inhibits biofilm formation

Vitamin D Deficiency & Tonsillitis

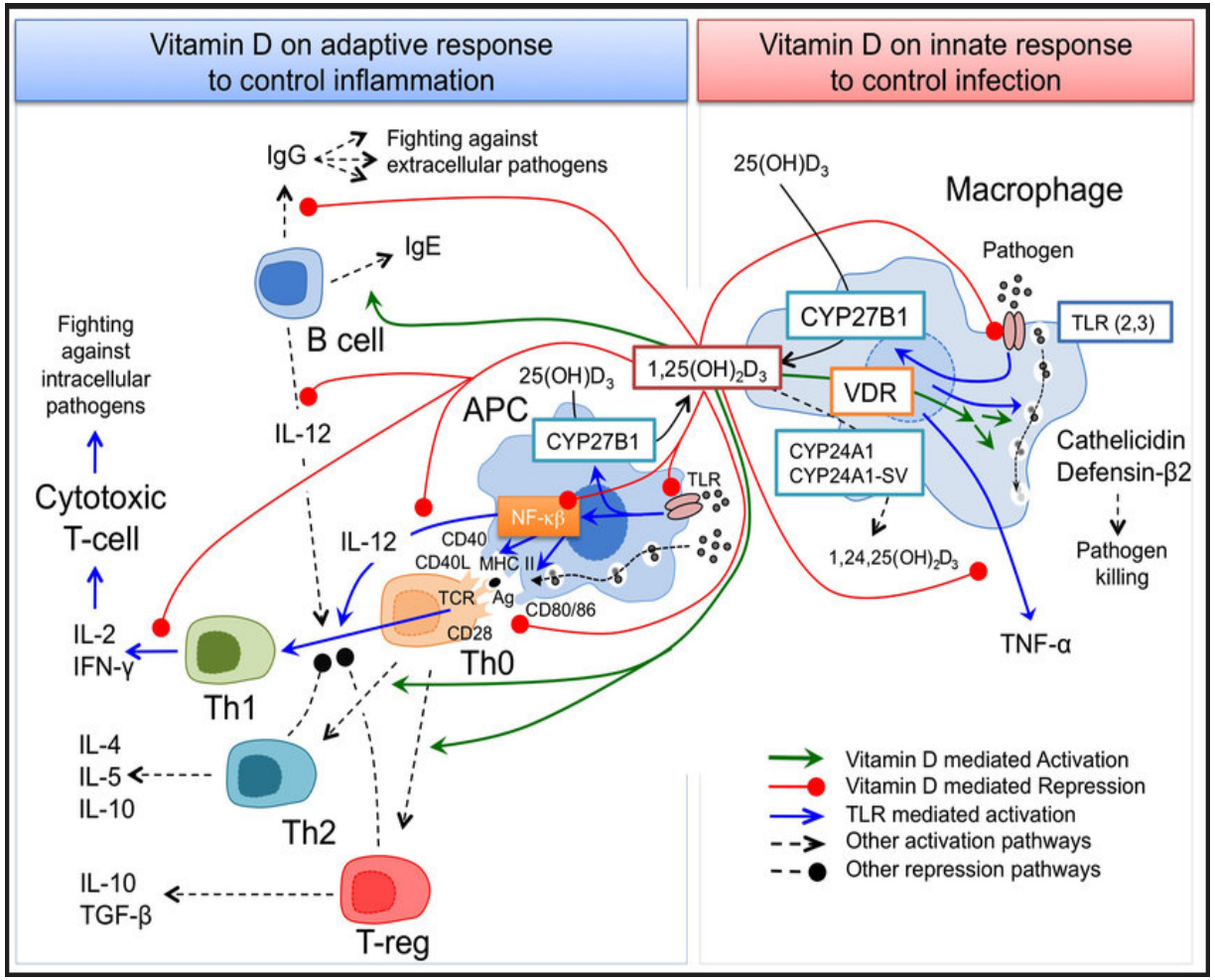
- Vitamin D deficiency may increase adenotonsillar hypertrophy via inadequate regulation of immune system

- Vitamin D . . .

-inhibits proliferation of activated lymphocytes

-reduces production of inflammatory cytokines

-promotes development of regulatory T-cells



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Fibla, J & Caruz, A. (2010). Vitamin D & HIV infection. *Soluble Factors Mediating Innate Immune Responses to HIV Infection,* 111-144.

Vitamin D Deficiency & Tonsillitis

- Retrospective, cross-sectional study
  - Children 4-12 yo
  - Symptoms for at least a year
  - OSA tool determined moderate to large impact on QOL
  - Serum 25(OH)D level

- Results:
  - 52.3% deficient
  - 71.4% insufficient

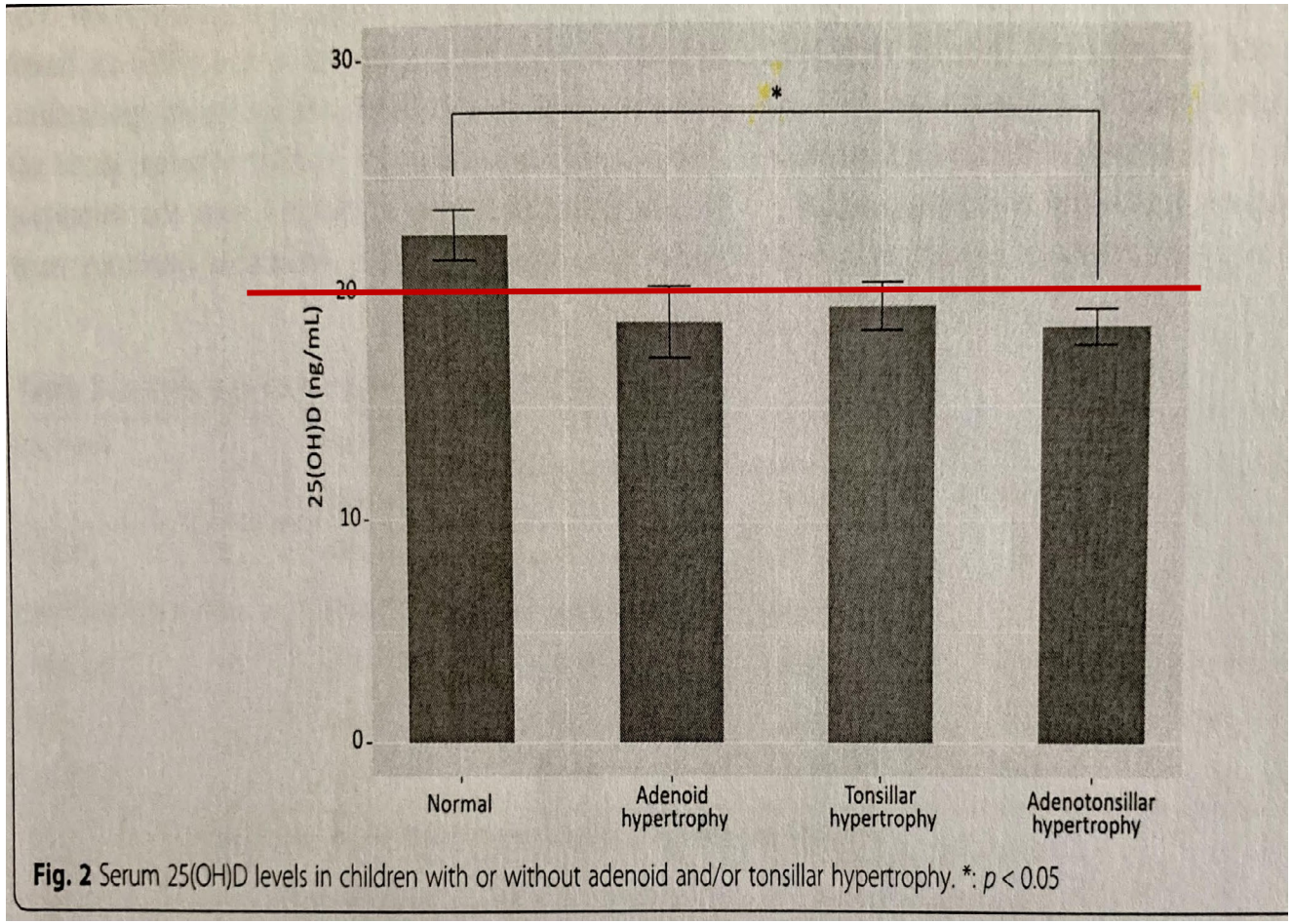

Fig. 2 Serum 25(OH)D levels in children with or without adenoid and/or tonsillar hypertrophy. *: $p < 0.05$

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Shin, etal. (2018). Is there an association between vitamin D deficiency and adenotonsillar hypertrophy in children with sleep-disordered breathing? *BMC Pediatrics, 18,* 196.

Vitamin D & Sinonasal Disease

- Correlation between Vitamin D deficiency and inflammation in NP patients
- Disease severity determined by SNOT 20 and CT scans
  - Median SNOT 20 score w/ polyposis=48 [moderate to severe NP disease]
  - Median CT score was 11 [mild to moderate NP disease]
- Obtained vitamin D and hs-CRP levels
- Results:
  - Strong negative correlation between D and hs-CRP
  - Severity of nasal polyps (SNOT 20) correlated negatively w/ D levels & positively w/ hs-CRP
  - Weak negative correlation for image staging and D
  - Weak positive correlation for image staging and hs-CRP
- Conclusions:
  - Significant systemic inflammation with lowered 25(OH)D in patients with NP
  - D supplementation might reduce systemic inflammation

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Chandrakar etal.(2020). 25-Hydroxyl Vitamin D Deficiency in Nasal Polyposis. *International Archives of Otorhinolaryngology, 24*(3):308.

Vitamin D & Sinonasal Disease

- Triple-blinded, placebo controlled clinical trial investigating effects of oral vitamin d3 on recurrence of polyposis after FESS
- 40 CRSwNP patients
- Routine postoperative treatment for all
- Treatment group= 4000 iU/d for 1 month
- SNOT22 & Meltzer endoscopic grading done at postoperative months 1,3, & 6

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Hashemian, F. etal. (2020). Effects of vitamin D supplementation on recurrence of nasal polyposis after endoscopic sinus surgery. *Iranian Journal of Otorhinolaryngology, 32*(1).

Vitamin D & Sinonasal Disease

Table 2: Endoscopic Meltzer Scoring in Control and Intervention Groups

	Placebo group		Vit.D tablet group		p-value (diff CI)
	MEAN	SD	MEAN	SD	
Pre-OP Meltzer score*	3.75	0.55	3.40	0.75	0.16 (-0.07-0.77)
Post-OP Meltzer score month 1**	0.30	0.47	0.00	0.00	0.11 (0.08-0.51)
Post-OP Meltzer score month 3#	1.35	0.93	0.20	0.41	< 0.001 (0.68-1.61)
Post-OP Meltzer score month 6##	2.65	0.93	0.50	0.60	< 0.001(1.64-2.65)

*t: 1.67, df:38, **t:2.85, df:38, #t: 5.04, df:38, ##t:8.63, df:38

Table 3: SNOT-22 Scoring in Drug and Placebo Group.

	Placebo group		Vit.D tablet group		p-value (diff CI)
	MEAN	SD	MEAN	SD	
Pre-OP SNOT-22 score*	67.05	17.44	63.4	19.45	0.53(-8.17-15.47)
Post-OP SNOT-22 score month 1**	18.80	14.05	12.55	9.57	0.10 (-1.44-13.94)
Post-Op SNOT-22 score month 3#	34.70	14.29	14.35	8.64	< 0.001(12.78-27.91)
Post-Op SNOT-22 score month 6##	47.45	13.55	16.25	10.16	< 0.001(23.53-38.86)

t:0.925, df:38, **t:1.64, df:38, #t:5.44, df:38, ##:t:8.63, df:38*

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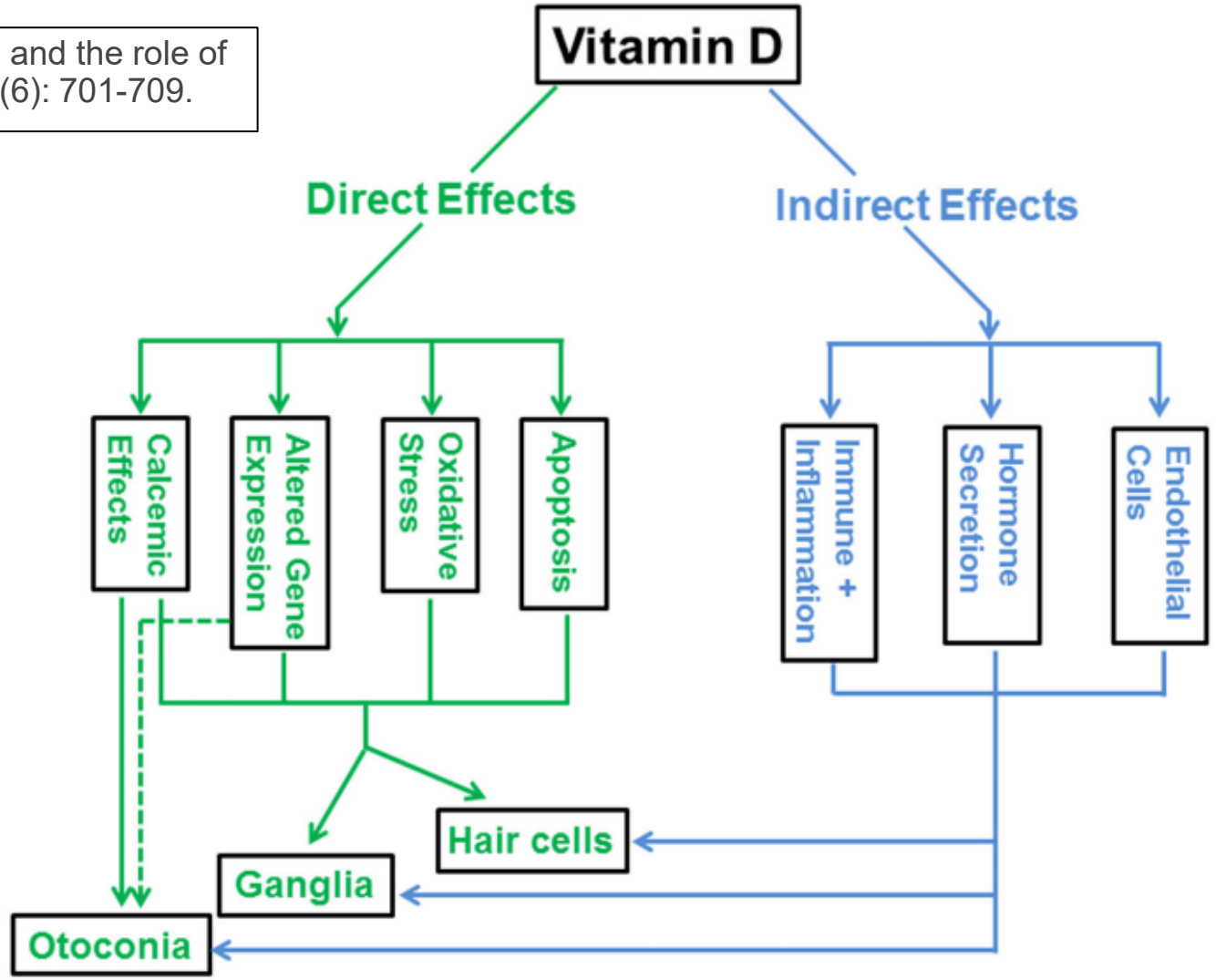
Hashemian, F. etal. (2020). Effects of vitamin D supplementation on recurrence of nasal polyposis after endoscopic sinus surgery. *Iranian Journal of Otorhinolaryngology, 32*(1).

Vitamin D → Inner ear

Buki, B, etal. (2019). The price of immune responses and the role of vitamin D in the inner ear. *Otology & Neurotology, 40*(6): 701-709.



Vit D deficiency: accelerated degeneration & aging

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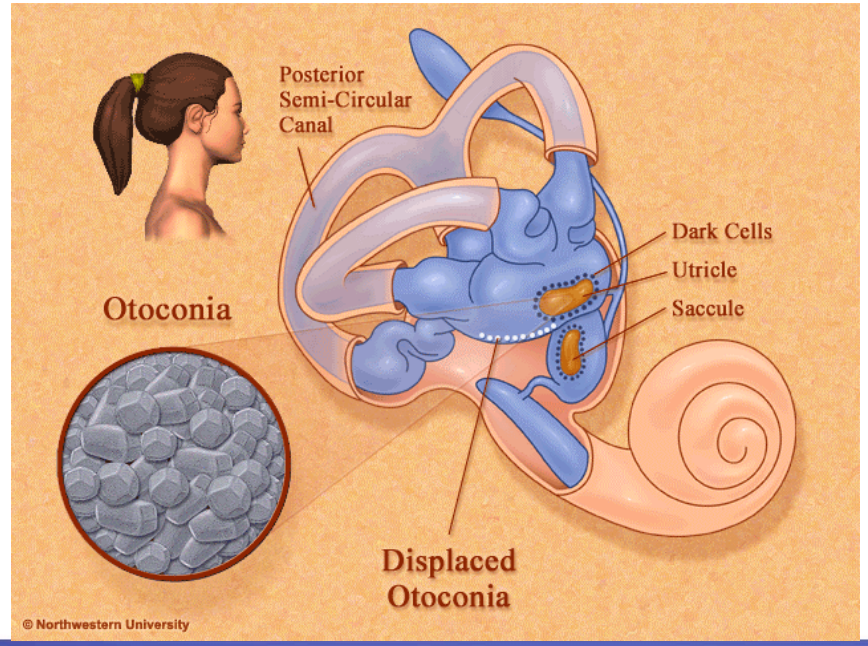
Vitamin D & BPPV

Association of impaired calcium metabolism & BPPV development

- Decreased bone mineral density observed more frequently in persons with BPPV than healthy controls
- Estrogen plays vital role in otoconia maintenance and development of BPPV
- Lower serum vitamin D associated with development of BPPV
- Vitamin D supplementation may reduce further BPPV attacks in persons with subnormal levels



Vitamin D & BPPV

Sanchez, JM, etal. (2022). Therapeutic effect of the corrections of vitamin D deficiency in patients with benign paroxysmal positional vertigo—A randomized clinical trial. *International Archives of Otorhinolaryngology.* DOI: 10.1055/s-0041-1730992

RCT of 35 patients with VDD & BPPV

- Control group treated w/ repositioning maneuvers
- Treatment group also supplemented
- Dizziness Handicap Index (DHI) at Diagnosis then at 6-12 months
- Results:
  - Mean D level 18.5 ng/ml ⟹ 26.2 ng/ml
  - Initial DHI mean scores similar
  - After supplementation:
    - DHI reduced in treatment group (10 ± 9)
    - DHI reduced in control group (36 ± 9)

Vitamin D Reposition

Patient serum 25/hidroxyvitamin D levels	Dosage of vitamin D	Duration of treatment	Maintenance	Dosage per day Valmetrol pills 1600 UI
< 10 ng/ml	180,000 UI	1 month	16,000 UI once a week	4 pills for 1 month 1.5 pills during 6 months
10-19 ng ml	16,000 UI	Once a week during 8-10 weeks	16,000 UI once a week	1.5 a day during 8-10 weeks 1.5 pill daily.
20-29 ng/ml	16,000 UI	Once a week during 5 weeks.	16,000 every 15 days during 5 weeks.	1.5 pills every day during 5 weeks. 1.5 pills every 15 days.

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Resources

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Resources (continued)

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Thank You!