PRINCE MAHIDOL
AWARD CONFERENCE

Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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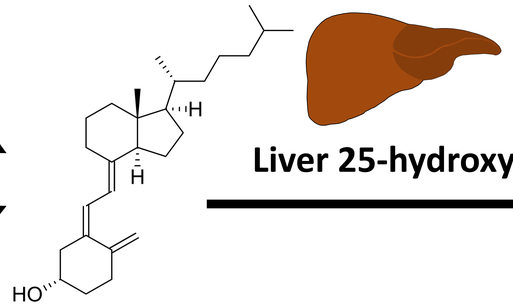
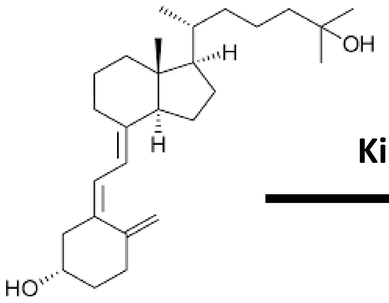
Diets & supplements

Sunlight exposure



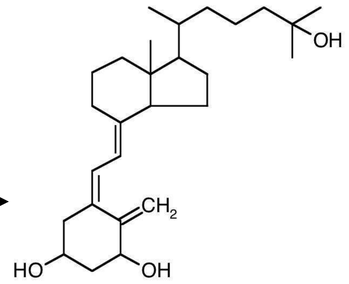
Vitamin D

Liver 25-hydroxylase



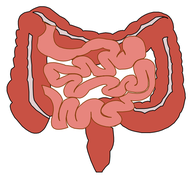
25-hydroxyvitamin D

Kidney 1α-hydroxylase

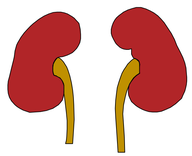


1,25-dihydroxyvitamin D

↑ Intestinal Ca and PO_4 absorption



↓ Urinary Ca excretion



↑ Bone remodeling

Non-skeletal effects

Vitamin D receptor

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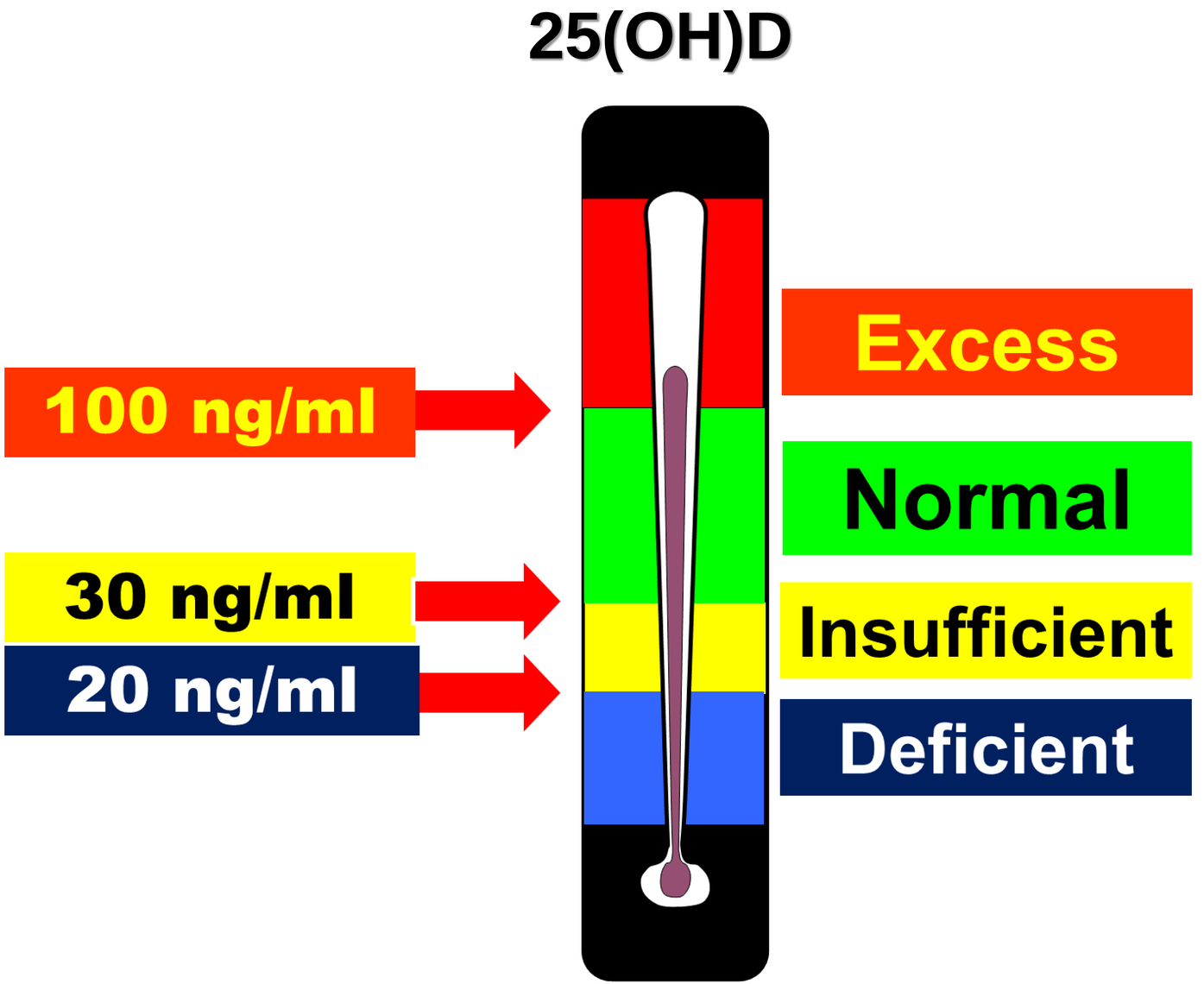

Endocrine Society Clinical Practice Guideline on Vitamin D 2011

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How common is vitamin D deficiency/insufficiency in Thailand?

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Original Article

Prevalence of Inadequate Vitamin D Status in Ambulatory Thai Patients with Cardiometabolic Disorders Who Had and Had No Vitamin D Supplementation

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Charoenngam N, Sriussadaporn S. J Med Assoc Thai 2018;101:739-52.

Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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Table 2. Vitamin D status in patients with cardiometabolic disorders compared between patients with and without vitamin D supplementation

Patients	Serum 25-OHD (ng/mL) Mean±SD	25-OHD <10 ng/mL n (%)	25-OHD <20 ng/mL n (%)	25-OHD <30 ng/mL n (%)
All patients (N=444)	26.12±10.10	12 (2.7%)	125 (28.2%)	254 (70.3%)
Patients with vitamin D supplementation (n=94; 21.2%)	27.56±9.72	2 (2.1%)	18 (19.1%)[a]	58 (61.7%)[b]
Patients without vitamin D supplementation (n=350; 78.8%)	25.72±10.18	10 (2.9%)	107(30.6%)[a]	253 (72.6%)[b]

A *p*-value<0.05 indicates statistical significance

[a] denotes statistically significant difference between patients with and without vitamin D supplementation (p=0.029)

[b] denotes statistically significant difference between patients with and without vitamin D supplementation (p=0.041)

Abbreviations: serum 25-OHD, serum 25-hydroxyvitamin D; SD, standard deviation

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Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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Table 7. Summary of prevalence of inadequate vitamin D status in different population subgroups in Thailand

Authors	Year	Sample size	Type of population	Prevalence of inadequate vitamin D status	Cut-point (ng/mL)	Method of 25-OHD measurement
Chailurkit. et al.	2011	2,641	Thai population	34.2-64.6%	<30	LC/MS/MS ($25\text{-}OHD_2+D_3$)
Chailurkit, et al.	2011	446	Thai elderly women	54.0%	<30	RIA ($25\text{-}OHD_2+D_3$)
Kruavit, et al.	2012	93	Thai nursing home residents	61.3%	<28	RIA ($25\text{-}OHD_2+D_3$)
Nimitphong, et al.	2013	1,449	Male subjects	13.9%	<20	LC/MS/MS
		541	Female subjects	43.1%		($25\text{-}OHD_2+D_3$)
Soontrapa, et al.	2015	66	Rural elderly males	13.6%	<40	ECLIA
		100	Urban elderly males	48.0%		($25\text{-}OHD_2+D_3$)
The present study	2018	444	Adult ambulatory patients with cardiometabolic disorders	70.3% 28.2%	<30 <20	ECLIA ($25\text{-}OHD_2+D_3$)

Abbreviations: 25-OHD, serum 25-hydroxyvitamin D; LC/MS/MS, liquid chromatography tandem mass spectrometry; RIA, radioimmunoassay; ECLIA, electrochemiluminescence immunoassay

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Sources of vitamin D

- Diet
  - D_2: Sun-exposed mushroom, fortified products
  - D_3: Cod liver oil, salmon, mackerel, tuna, fortified products
- Sunlight
  - Winter: No vitamin D_3 synthesis at latitude >33°
  - Spring, Summer, Fall: vitamin D_3 production 10 am – 3 pm
- Supplement

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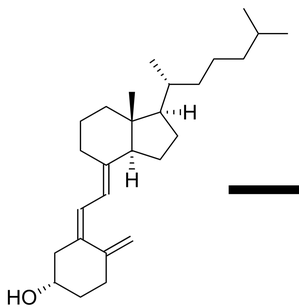
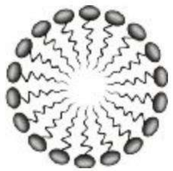
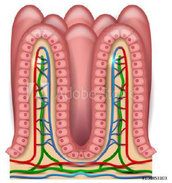


Vitamin D

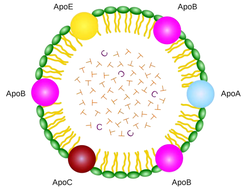
Bile acid



Micelles



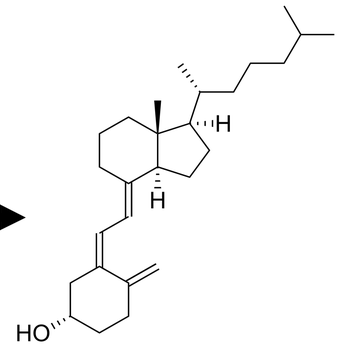
Duodenal villi



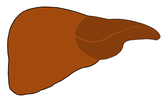
Chylomicrons

40% cleared in the lipoprotein bound fraction

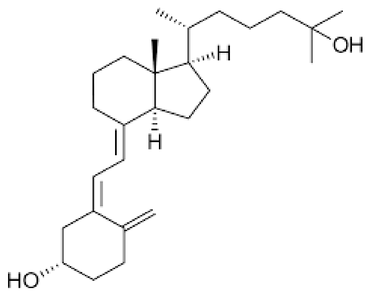
Lymphatic system



Circulating vitamin D



Liver 25-hydroxylase



Circulating 25-hydroxyvitamin D_3

- Bile acid insufficiency
- IBD
- Cystic fibrosis
- Chronic pancreatitis

- Gastric bypass surgery
- Celiac disease
- Villous atrophy
- SIBO

- Lymphangiectasia

Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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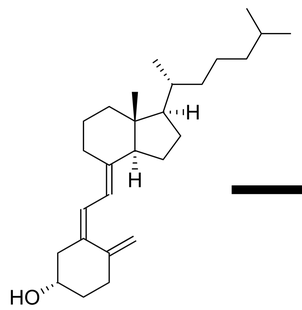
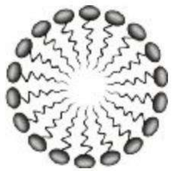
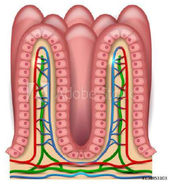
Bile acid



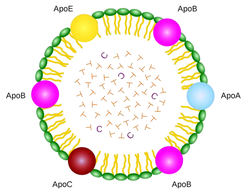
Vitamin D



Micelles



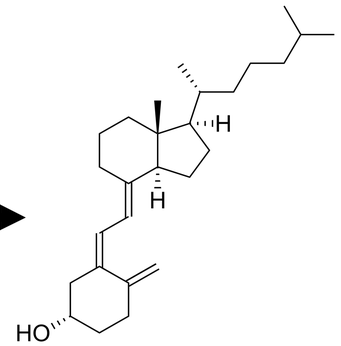
Duodenal villi



Chylomicrons

40% cleared in the lipoprotein bound fraction

Lymphatic system



Circulating vitamin D

- Bile acid insufficiency
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- Gastric bypass surgery
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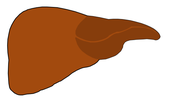
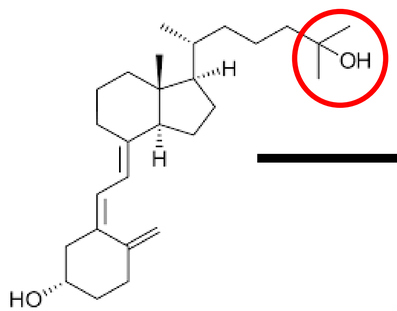
- Lymphangiectasia

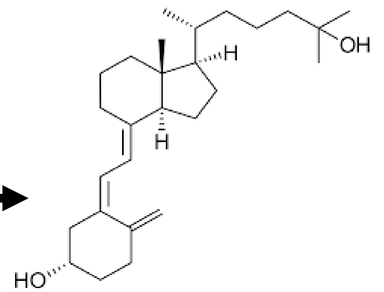


Liver 25-hydroxylase



25-hydroxyvitamin D_3

Portal system



Circulating 25-hydroxyvitamin D_3

Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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A Pilot Clinical Trial to Evaluate the Pharmacokinetics of Orally Administered 25-hydroxyvitamin D_3 and Vitamin D_3 in Healthy Adults and Adults With a History of Intestinal Malabsorption

Study design: Randomized double-blinded crossover study

Subjects: 10 healthy adults and 6 malabsorptive patients with vitamin D insufficiency or deficiency

Eligibility criteria

- Age ≥18 years old (healthy or with a history of intestinal malabsorption)
- No conditions affecting vitamin D metabolism
- Vitamin D deficiency/insufficiency defined by serum total 25(OH)D <30 ng/mL
- Not taking vitamin D supplement within 2 weeks
- Not pregnant
- No contraindications to oral vitamin D

Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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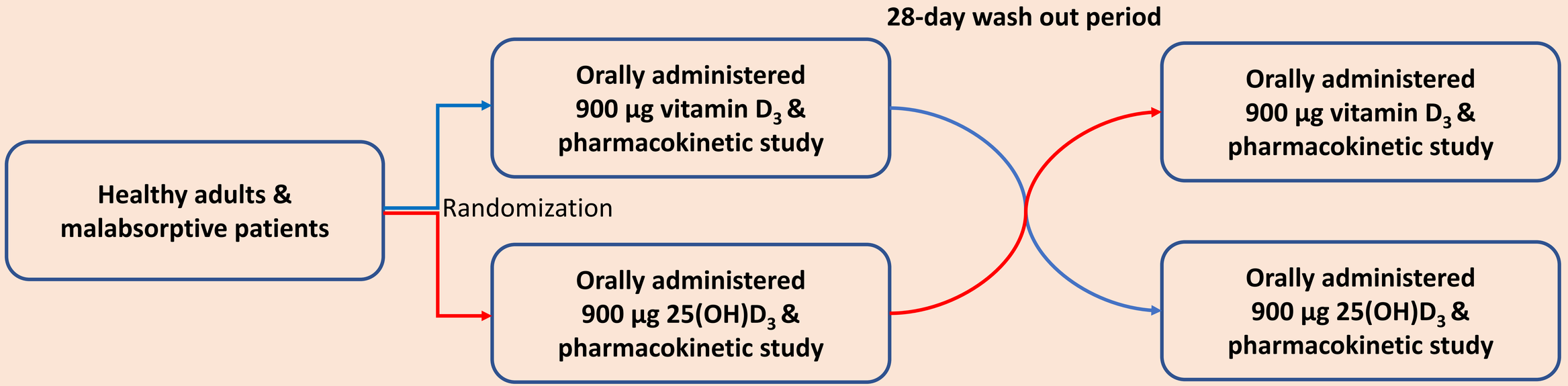
Intervention: Pharmacokinetic studies of orally administered 900 µg vitamin D_3 and 900 µg 25(OH)D_3



Serum measurement	Baseline	2 h	4 h	6 h	8 h	12 h	1 d	2 d	3 d	7 d	14 d
Vitamin D (D_2 & D_3)	X	X	X	X	X	X	X	X	X	X	X
25(OH)D [25(OH)D_2 & 25(OH)D_3]	X	X	X	X	X	X	X	X	X	X	X
Ca, PO_4, iPTH, albumin, Cr	X										X

Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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Results

- **Baseline characteristics of healthy adults and malabsorptive patients**

	Healthy participants (N = 10)	Malabsorptive patients (N = 6)	p-value
Age	32.3 ± 2.7	46.5 ± 4.1	0.010*
Number of female participants	8 (80 %)	6 (100 %)	
Body mass index (kg/m^2)	27.0 ± 2.1	32.7 ± 4.1	0.192
Ethnicity			
• Caucasian	5 (50 %)	4 (67 %)	
• Hispanic	0 (0 %)	1 (17 %)	
• Asian	2 (20 %)	0 (0 %)	
• Black	3 (30 %)	1 (17 %)	
Diagnosis			
• Gastric bypass surgery		4 (67 %)	
• Intestinal lymphangiectasia		1 (17 %)	
• Ulcerative colitis		1 (17 %)	

Data were expressed as mean ± SEM

Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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Results

- **Baseline characteristics of healthy adults and malabsorptive patients**

	Healthy participants (N = 10)	Patients with fat malabsorption (N = 6)	p-value
Vitamin D_2 (ng/mL)	0.0 ± 0.0	0.0 ± 0.0	N/A
Vitamin D_3 (ng/mL)	0.0 ± 0.0	1.6 ± 1.0	0.183
Total 25-hydroxyvitamin D (ng/mL)	17.1 ± 2.3	14.7 ± 3.4	0.554
25-hydroxyvitamin D_2 (ng/mL)	0.4 ± 0.4	4.2 ± 3.1	0.284
25-hydroxyvitamin D_3 (ng/mL)	16.7 ± 2.1	10.5 ± 4.2	0.228
Intact PTH (pg/mL)	41.5 ± 5.4	74.0 ± 16.9	0.116
Total calcium (mg/dL)	9.4 ± 0.1	9.4 ± 0.1	0.796
Phosphate (mg/dL)	3.9 ± 0.3	4.0 ± 0.3	0.736
Creatinine (mg/dL)	0.8 ± 0.03	0.7 ± 0.04	0.103
eGFR (mL/min/1.73m^2)	106.8 ± 4.7	104.0 ± 6.7	0.733
Glucose (mg/dL)	83.1 ± 7.5	89.8 ± 8.8	0.580
Albumin (g/dL)	4.4 ± 0.08	4.1 ± 0.05	0.027*

*Data were expressed as mean ± SEM

Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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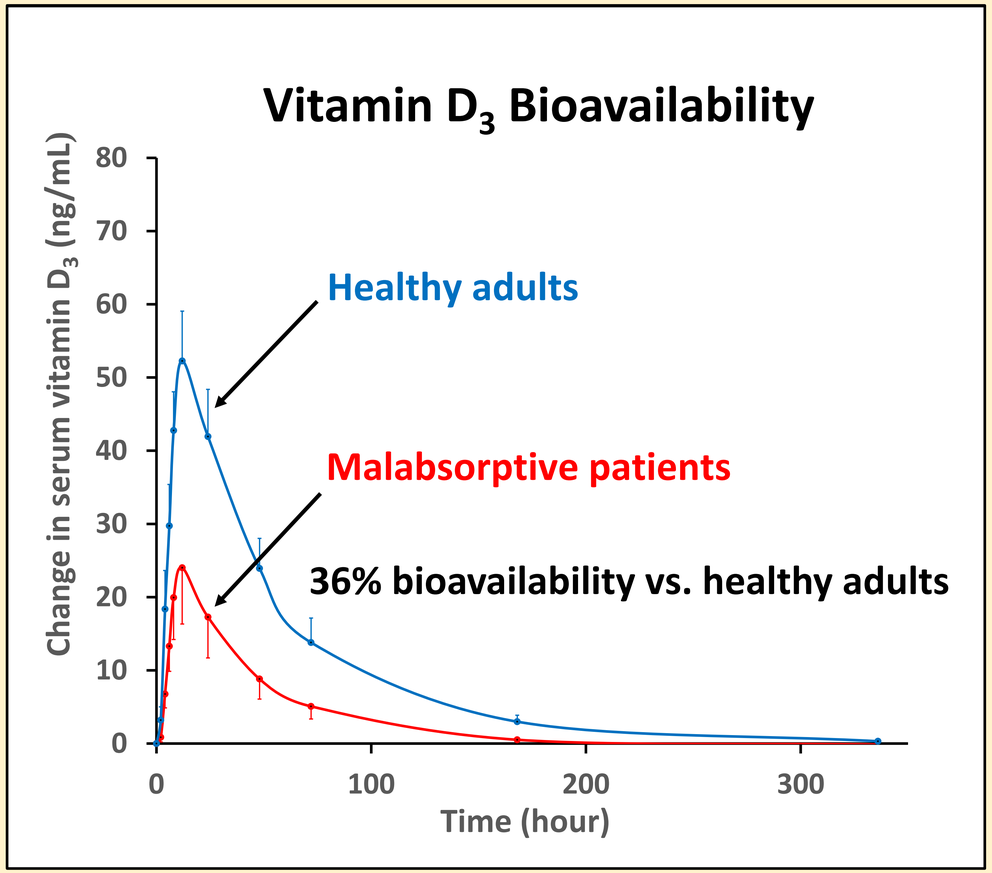
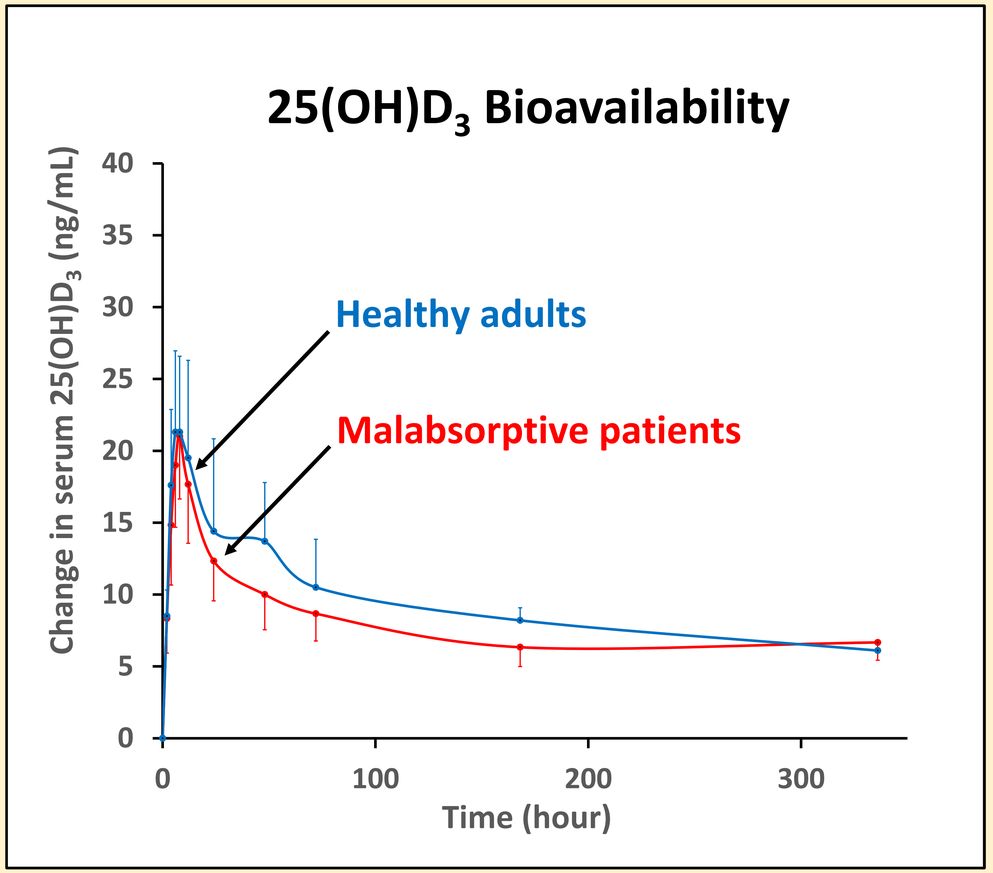
Results

- **Pharmacokinetic studies of orally administered 900 µg vitamin D_3 and 900 µg 25(OH)D_3**





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Pharmacokinetic Evaluation of Vitamin D_3 and 25-Hydroxyvitamin D_3 in Normal and Malabsorptive Adults

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Results

- **Pharmacokinetic studies of orally administered 900 µg vitamin D_3 and 900 µg 25(OH)D_3**

Pharmacokinetic parameters	900 µg vitamin D_3 arm			900 µg 25(OH)D_3 arm		
	Healthy adults (N = 10)	Malabsorptive patients (N = 6)	p-value	Healthy adults (N = 10)	Malabsorptive patients (N = 6)	p-value
AUC (ng·hr /mL)	3258 ± 496	1177 ± 425	0.022*	3128 ± 545	2667 ± 735	0.562
C_{max} (ng/mL)	53.5 ± 6.0	24.3 ± 8.4	0.016*	23.1 ± 4.6	23.2 ± 6.8	1.000
T_{max} (hr)	10.4 ± 0.7	11.3 ± 0.7	0.345	11.2 ± 4.1	5.3 ± 0.7	0.031*
$T_{1/2}$ (hr)	31.4 ± 3.3	28.7 ± 1.5	0.713	60.6 ± 7.9	65.7 ± 29.9	0.313
C_{trough} (ng/mL)	0.3 ± 0.3	0.1 ± 0.1	0.220	6.1 ± 1.3	6.7 ± 1.5	0.875

Data were expressed as mean ± SEM

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Conclusions

- Malabsorptive patients who are unable to efficiently form micelles and chylomicrons have difficulty absorbing vitamin D.
- Our observations that the bioavailability of 900 µg 25(OH)D_3 was not different between malabsorptive patients and healthy adults support that the more water-soluble 25(OH)D_3 can be absorbed directly into the portal system.
- Orally administered 25(OH)D_3 would be a good choice for treatment of vitamin D deficiency in malabsorptive patients.
- Further studies should be conducted to evaluate the bioavailability of 25(OH)D in a larger number of patients with other malabsorptive conditions.

ANTICANCER RESEARCH *40*: 551-556 (2020)
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The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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Department of Medicine, Section of Endocrinology, Nutrition, and Diabetes, Vitamin D, Skin and Bone Research Laboratory, Boston University Medical Center, Boston, MA, U.S.A.

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The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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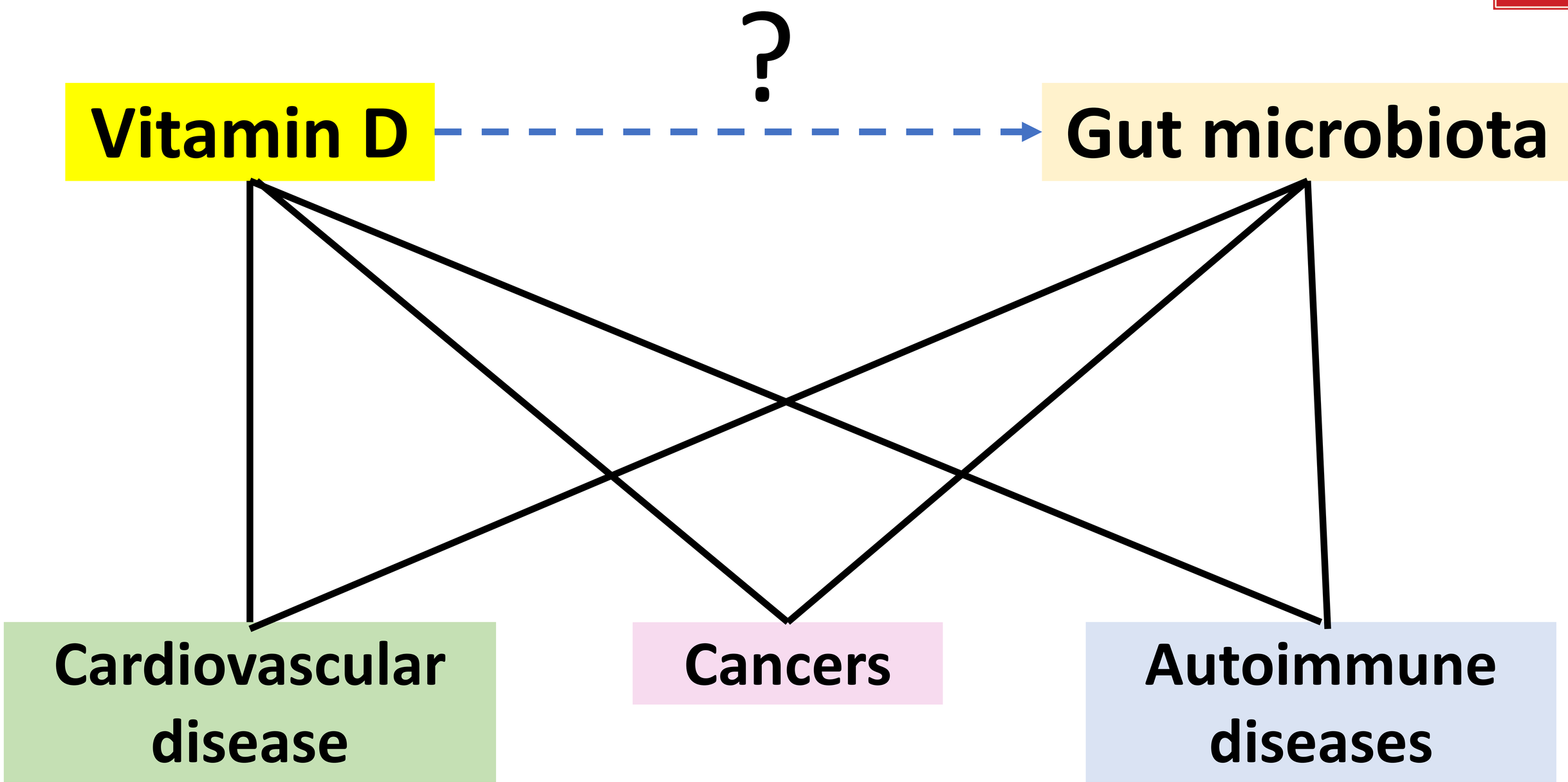

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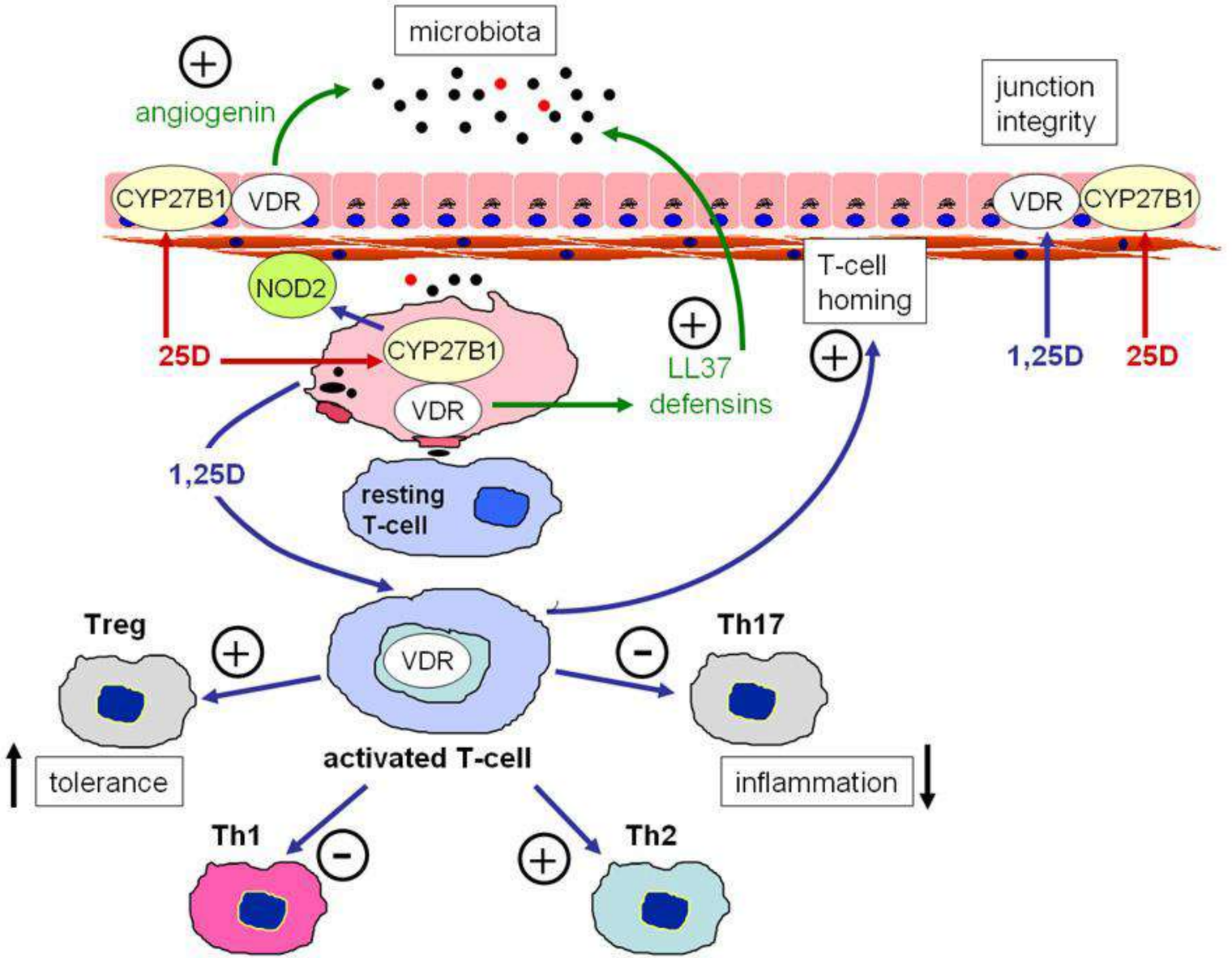

Ref: UCLA Vitamin D Research Lab: https://www.uclahealth.org/ortho/non-classical

The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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Disassociation of Vitamin D's Calcemic Activity and Non-calcemic Genomic Activity and Individual Responsiveness: A Randomized Controlled Double-Blind Clinical Trial

Arash Shirvani, Tyler Arek Kalajian, Anjeli Song & Michael F. Holick*

The aims of this randomized controlled double-blind clinical trial were to assess the impact of vitamin D supplementation on calcium metabolism and non-calcemic broad gene expression by relating them to the individual's responsiveness to varying doses of vitamin D_3. Thirty healthy adults were randomized to receive 600, 4,000 or 10,000 IU/d of vitamin D_3 for 6 months. Circulating parathyroid hormone (PTH), 25(OH)D, calcium and peripheral white blood cells broad gene expression were evaluated. We observed a dose-dependent increase in 25(OH)D concentrations, decreased PTH and no change in serum calcium. A plateau in PTH levels was achieved at 16 weeks in the 4000 and 10,000 IU/d groups. There was a dose-dependent 25(OH)D alteration in broad gene expression with 162, 320 and 1289 genes up- or down-regulated in their white blood cells, respectively. Our results clearly indicated that there is an individual's responsiveness on broad gene expression to varying doses of vitamin D_3. Vitamin D_3 supplementation at 10,000 IU/d produced genomic alterations several fold higher than 4,000 IU/d even without further changes in PTH levels. Our findings may help explain why there are some inconsistency in the results of different vitamin D's clinical trials.

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The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

Study design: Randomized, double-blinded, dose-response pilot study

Subjects: 20 healthy adults with vitamin D insufficiency or deficiency

- Age ≥18 years old (healthy or with a history of intestinal malabsorption)
- No conditions affecting vitamin D absorption and metabolism
- BMI <30 kg/m^2
- Vitamin D deficiency/insufficiency defined by serum total 25(OH)D <30 ng/mL
- Not taking vitamin D supplement ≥ 600 IUs/d
- Not pregnant
- No contraindications to oral vitamin D
- No direct exposure to artificial UVB or solar radiation during the past month for >8 hours

The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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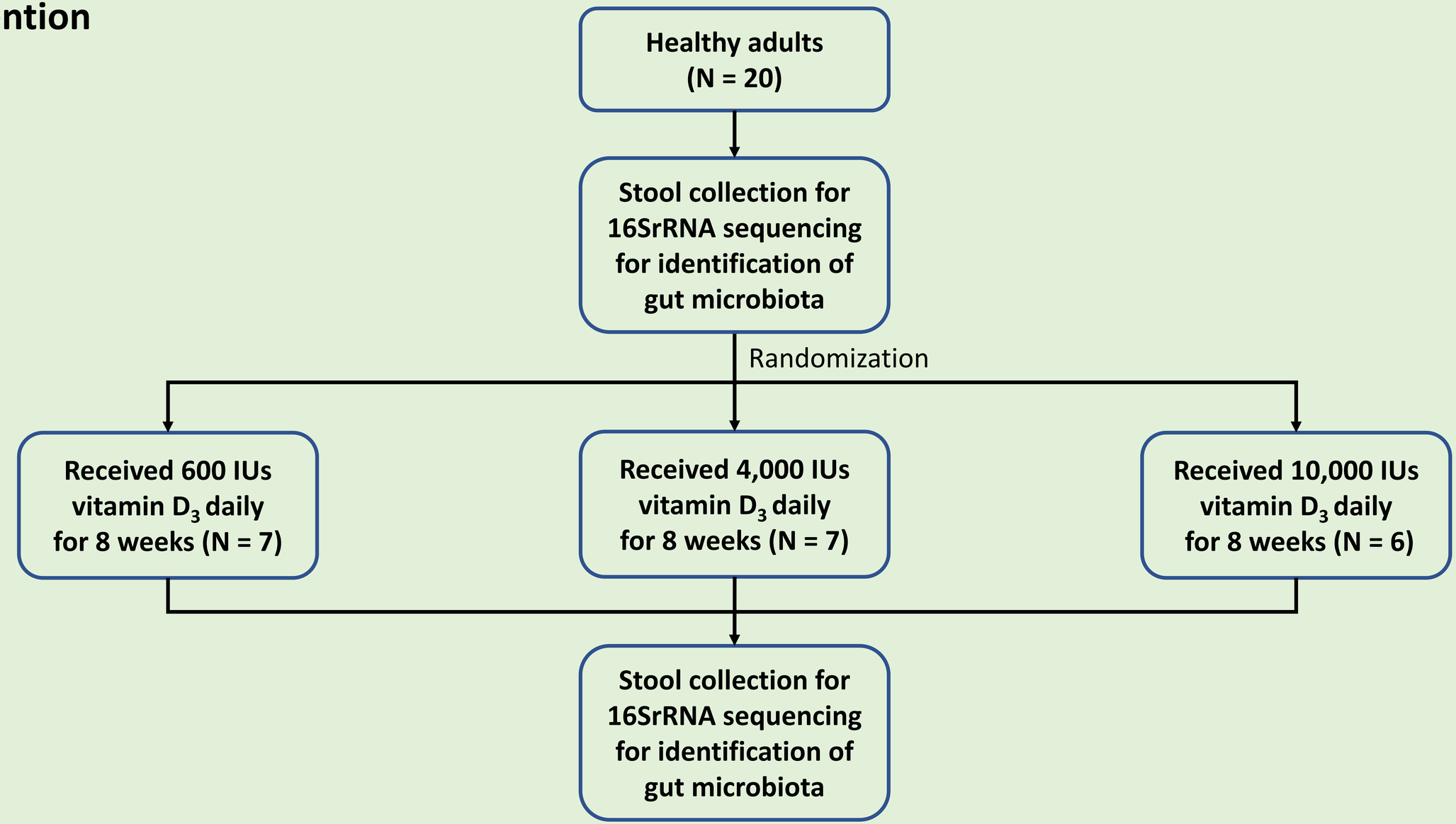
Intervention



The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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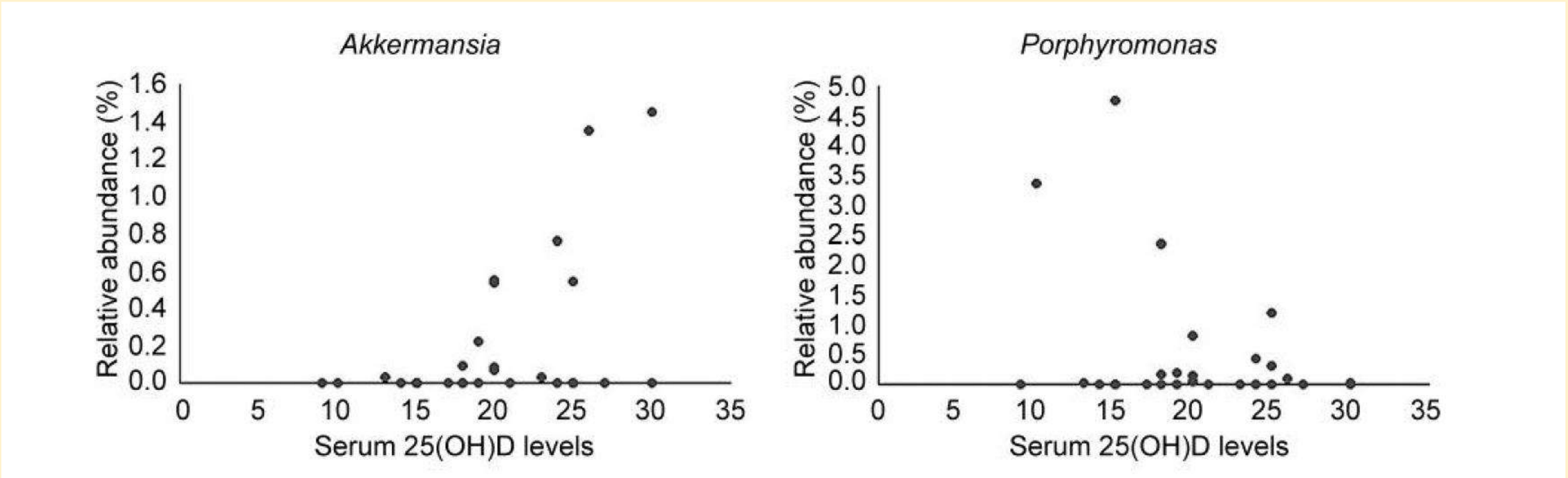
Results

Relative abundance of *Akkermansia* and *Porphyromonas* of the participants at various levels of serum 25(OH)D at baseline of the study



R = 0.684, p = 0.001

R = -0.435, p = 0.043

The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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Mini Review

A next-generation beneficial microbe: *Akkermansia muciniphila*

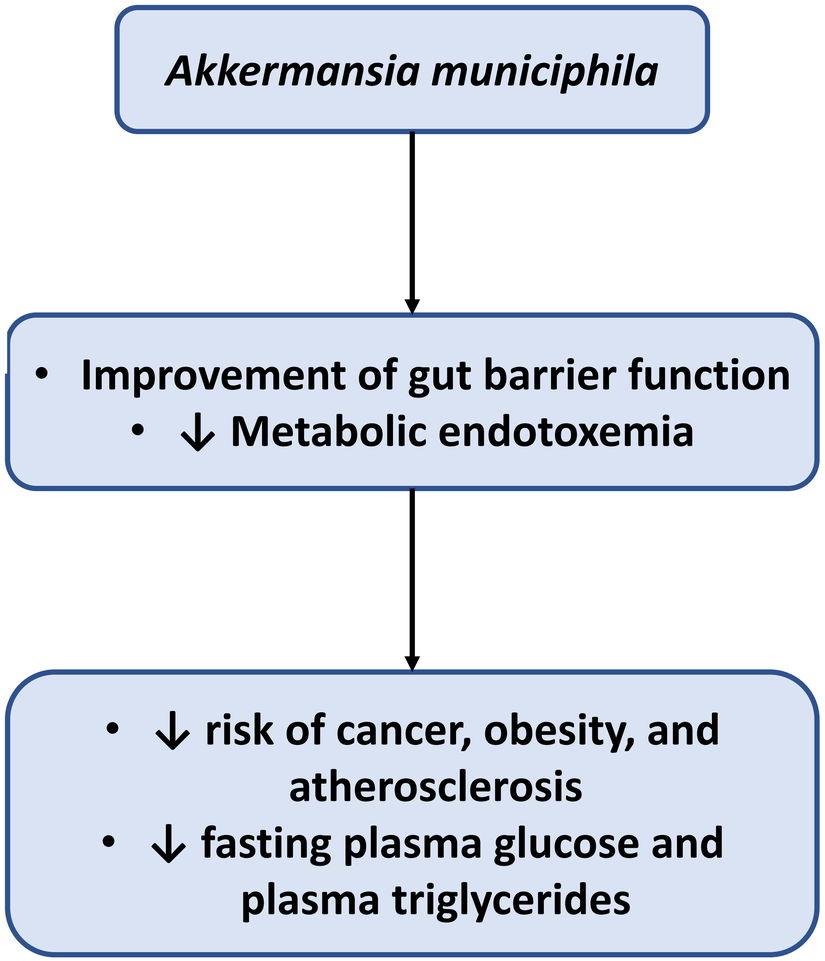
Yuji Naito,[1,2,*] Kazuhiko Uchiyama[1] and Tomohisa Takagi[1]

[1]Molecular Gastroenterology and Hepatology and [2]Department of Endoscopy and Ultrasound Medicine, University Hospital, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan

(Received 11 May, 2018; Accepted 13 May, 2018; Published online 20 June, 2018)

There have been many reports on the roles of intestinal flora and intestinal environment in health promotion and disease prevention. Beneficial bacteria such as *Bifidobacterium* and lactic acid-producing bacteria have been shown to improve the intestinal environment, and yield a good effect on metabolism, immunity and nerve response. In this review, in addition to these beneficial bacteria, we introduced *Akkermansia muciniphila* as a next-generation beneficial microbe. Several reports indicate that *Akkermansia muciniphila* affects glucose metabolism, lipid metabolism, and intestinal immunity, and that certain food ingredients such as polyphenols may increase the abundance of *Akkermansia muciniphila* in the gut.

Key Words: *Akkermansia muciniphila*, diabetes, polyphenols, cancer immunotherapy



The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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Journal of PERIODONTAL RESEARCH

J Periodont Res 2016; 51: 359–365

JOURNAL OF PERIODONTAL RESEARCH
doi:10.1111/jre.12315

Vitamin D inhibits the growth of and virulence factor gene expression by *Porphyromonas gingivalis* and blocks activation of the nuclear factor kappa B transcription factor in monocytes

D. Grenier[1], M.-P. Morin[1], J. Fournier-Larente[1], H. Chen[2]
[1]Oral Ecology Research Group, Faculty of Dentistry, Université Laval, Quebec City, QC, Canada and [2]Department of Stomatology, Hubei University of Science and Technology, Xianning, Hubei, China

Grenier D, Morin M-P, Fournier-Larente J, Chen H. Vitamin D inhibits the growth of and virulence factor gene expression by Porphyromonas gingivalis *and blocks activation of the nuclear factor kappa B transcription factor in monocytes. J Periodont Res 2016; 51: 359–365. © 2015 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd*

Table 1. The relationship between 25-hydroxyvitamin D_3 (25(OH)D_3) concentrations in the plasma and periodontal diseases.

Authors, Year of Publication	Study Design	Sample Size	Outcome Measure	Outcome Measurement	Results
Dietrich et al., 2004 [13]	cross-sectional	11 202	Periodontitis	attachment level	decreased concentration is associated with changed (poor) periodontal condition
Dietrich et al., 2005 [14]	cross-sectional	6 700	Gingivitis	level of gingival inflammation (bleeding index)	decreased concentration is associated with gingival inflammation and higher bleeding index
Borggess et al., 2011 [15]	case-control	123 cases, 123 controls	PD in pregnant women	probing depth, bleeding index	women with vitamin D deficiency in the plasma (<75 nmol/L) are more prone to chronic periodontitis during pregnancy
Zhou et al., 2012 [16]	case-control	193 cases, 181 controls	PD and chronic obstructive pneumonia	pockets depth, periodontal attachment level, gingival bleeding index, teeth number	decreased concentration is associated with poor periodontal condition
Teles et al., 2012 [11]	exploratory	56	Chronic periodontitis	bleeding index, probing depth, periodontal attachment level, teeth number	decreased concentration is associated with poor periodontal condition
Antonoglou et al., 2013 [17]	comprehensive	80	Chronic periodontitis with type 1 diabetes	amount of plaque, probing depth, attachment level	authors did not find correlation between 25(OH)D3 concentration in the plasma and chronic periodontitis
Millen et al., 2013 [18]	multi-center	920	Chronic periodontitis in postmenopausal age	X-ray, attachment level, probing depth, bleeding index	decreased concentration is associated with chronic periodontitis
					increased concentration is associated with gingival bleeding
Liu et al., 2009 [19]	preliminary	178	Aggressive periodontitis	probing depth, attachment level, bleeding index	increased concentration is associated with aggressive periodontitis
Zhang et al., 2013 [20]	case-control	44 cases, 32 controls	Generalized aggressive periodontitis	probing depth, attachment level, bleeding index	increased concentration is associated with generalized aggressive periodontitis

The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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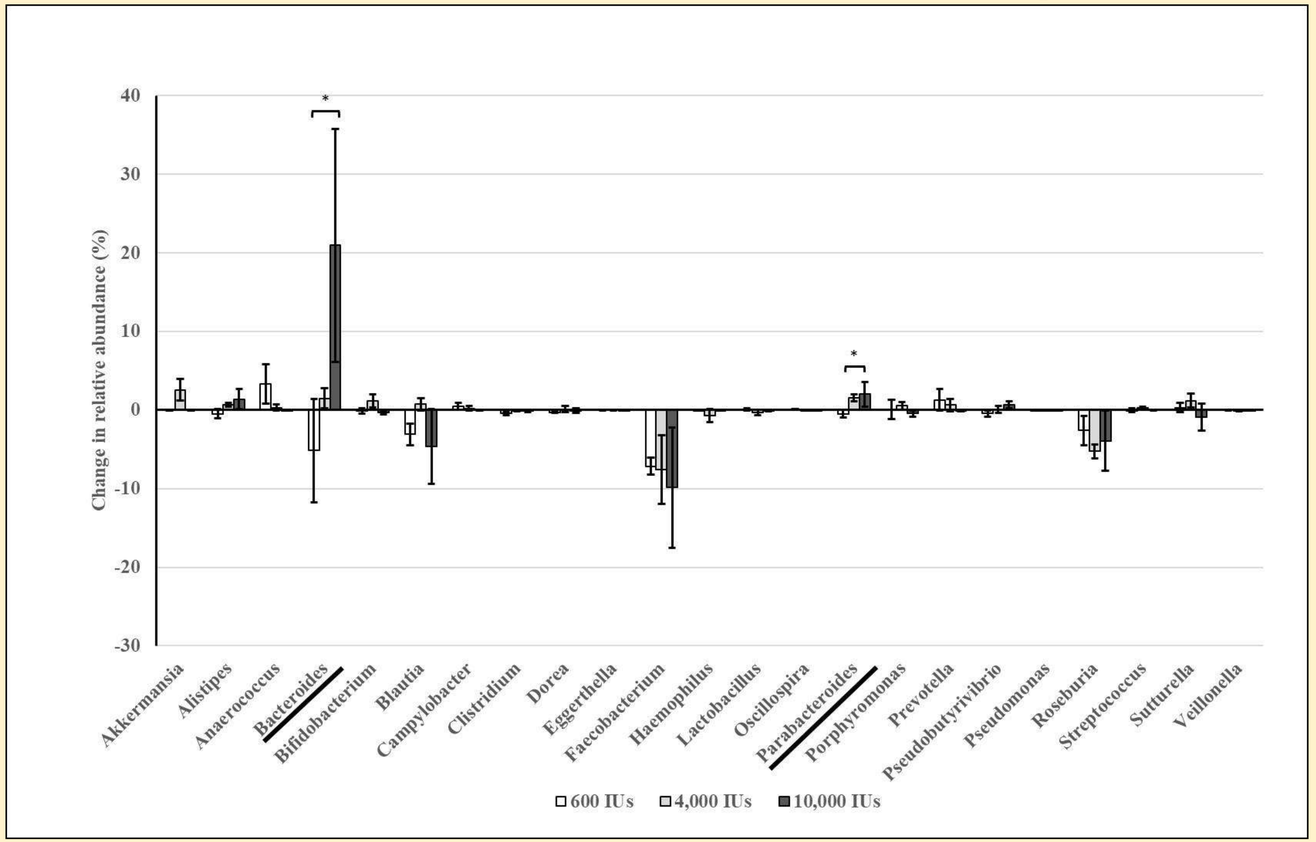
Results

Changes in relative abundance of clinically relevant bacterial genera in participants receiving various doses of vitamin D_3 for 8 weeks



Data are expressed as mean ± SEM

Dose-dependent increase in relative abundance of *Bacteroides* and *Parabacteroides*

The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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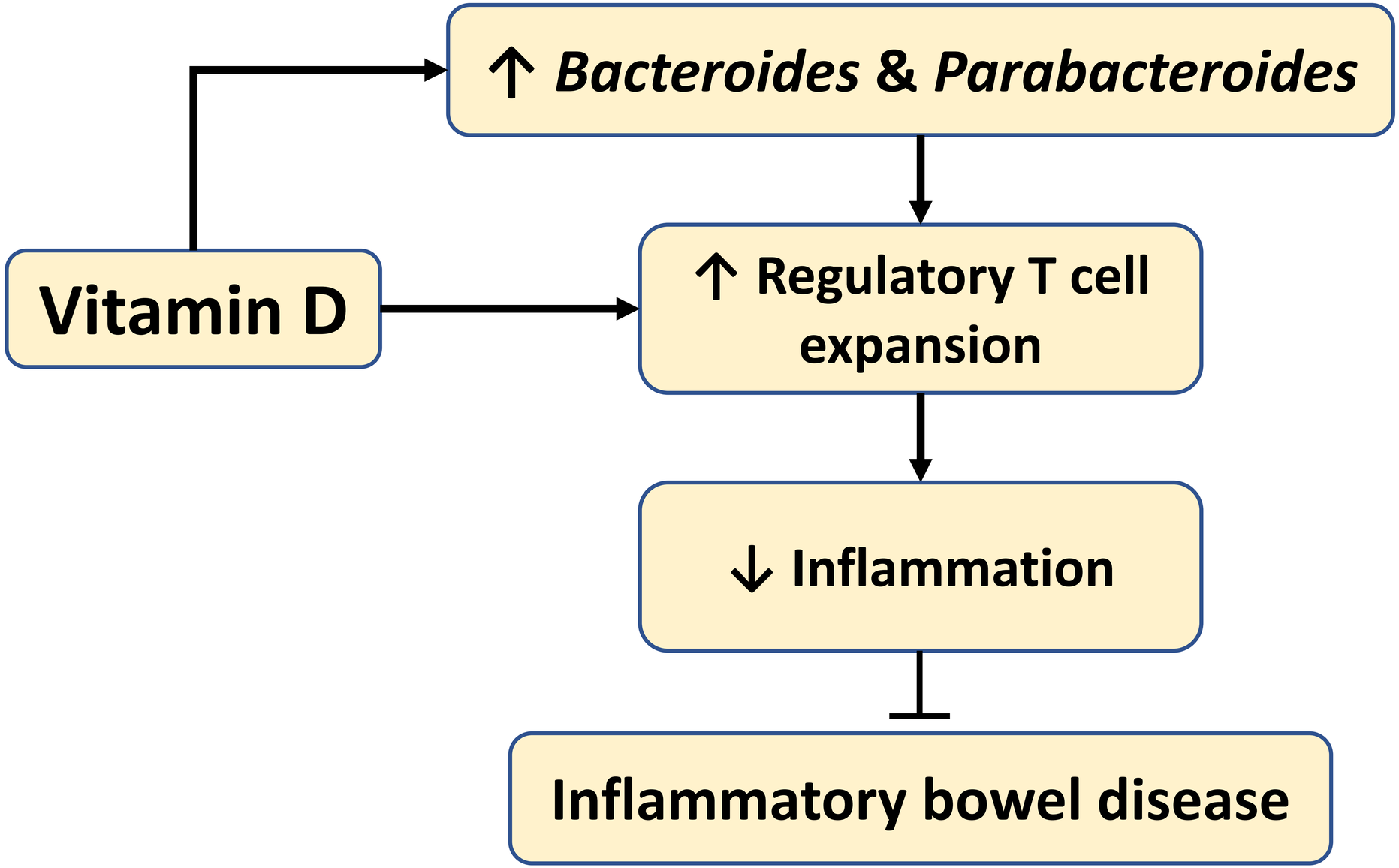

The Effect of Various Doses of Oral Vitamin D_3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-blinded, Dose-response Study

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Systematic Review and Meta-Analysis

Medicine®

OPEN

Efficacy of vitamin D in treatment of inflammatory bowel disease

A meta-analysis

Jinzhong Li, MD[a], Ning Chen, MD[b], Dan Wang, MD[a], Jie Zhang, PhD[b], Xiaobing Gong, PhD[a,*]

Abstract

Background: Vitamin D (VitD) deficiency is prevalent in patient with inflammatory bowel disease (IBD). Recent studies have found that VitD can induce and maintain IBD remission through antibiosis, anti-inflammatory, and repair of intestinal mucosal barriers, thus improving the patient's disease activity and quality-of-life. The purpose of this meta-analysis is to evaluate the therapeutic effect and safety of VitD in the treatment of IBD.

Methods: Published randomized controlled trials (RCTs) were included from electronic databases (PubMed, Embase, Cochrane library, Web of Science, and so forth). Cochrane handbook was applied to evaluate the methodological quality. The levels of 25(OH) D3, relapse rate, inflammation index, and adverse events were compared between the experimental group and the control group (placebo group). All statistical analyses were directed by Revman 5.3 software and statistical significance was defined as $P < .05$.

Results: Eighteen RCTs involved 908 patients were included. Meta-analysis showed that VitD improved the 25(OH)D3 levels more significantly than the control group (ng/mL, weighted mean deviation [WMD] = 7.85, 95% CI (5.52, 10.18), $P < .000001$), and compared with lower doses, there were significant differences increasing 25(OH)D3 levels (WMD = 11.19, 95% CI [4.73, 17.65], $P = .0007$) in high-dose VitD treatment while there was no significant difference in the adverse events between 2 groups (WMD = 1.56, 95% CI [0.74, 3.29], $P = .24$). VitD reduced the relapse rate more significantly than the control group, but there were no significant differences between the low-dose and high-dose vitamin D treatment. The erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP) of the VitD and the control group showed no statistically significant difference (ESR [mm/h]: WMD = −0.22, 95% CI [−5.73, 5.29], $P = .94$; hsCRP (mg/dL): WMD = −0.53, 95% CI [−1.68, 0.62], $P = .37$).

Conclusions: The treatment of VitD in patients with IBD can improve the level of 25(OH)D3 and control the relapse rate of the disease, whose clinical curative effect is more accurate. Thus VitD should be recommended for the treatment of IBD, at least as an adjunctive treatment.

Abbreviations: CD = Crohn disease, DCs = dendritic cells, ESR = erythrocyte sedimentation rate, hsCRP = high-sensitivity C-reactive protein, IBD = inflammatory bowel disease, NF-*k*B = nuclear factor kappa B, NOD2 = nucleotide-binding oligomerization domain protein 2, RCTs = randomized controlled trials, TNF-*a* = tumor necrosis factor-*a*, UC = ulcerative disease, VDR = vitamin D receptor, VitD = Vitamin D.

Keywords: Crohn disease, inflammatory bowel disease, meta-analysis, systematic review, ulcerative colitis

Osteoporosis International
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REVIEW

Oral vitamin D_3 supplementation increases serum fibroblast growth factor 23 concentration in vitamin D-deficient patients: a systematic review and meta-analysis

N. Charoenngam [1,2] · P. Rujirachun [3] · M.F. Holick [2] · P. Ungprasert [4]

Received: 21 April 2019 / Accepted: 18 July 2019

Oral vitamin D_3 supplementation increases serum fibroblast growth factor 23 concentration in vitamin D-deficient patients: a systematic review and meta-analysis

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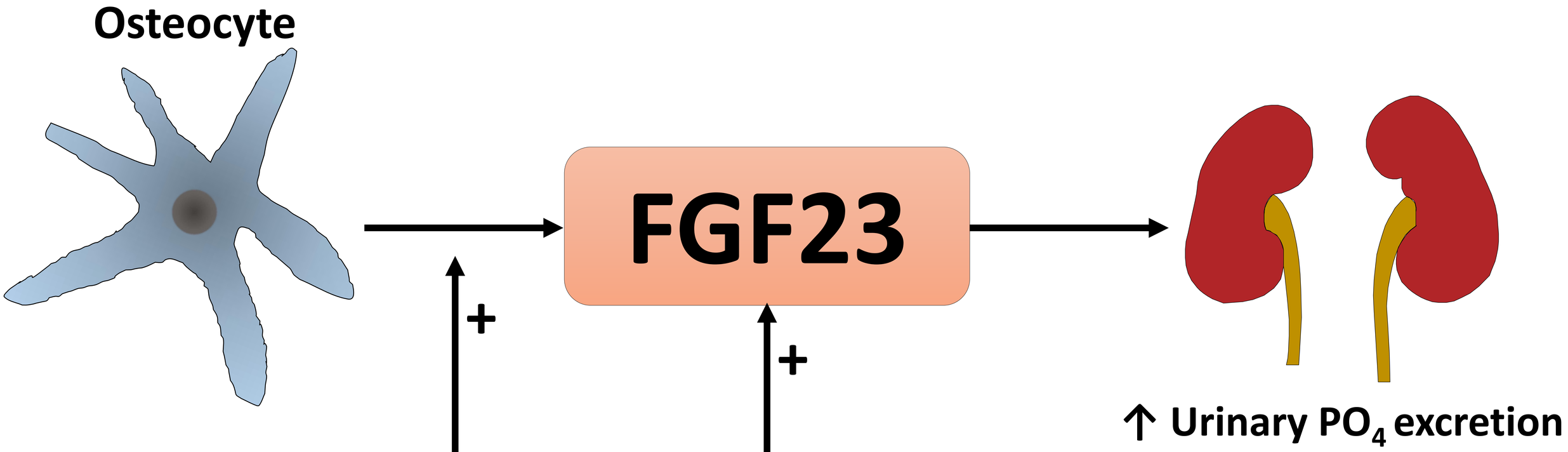

Oral vitamin D_3 supplementation increases serum fibroblast growth factor 23 concentration in vitamin D-deficient patients: a systematic review and meta-analysis

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Study or Subgroup	Post-treatment Mean	SD	Total	Pre-treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Garcia-lopes et al. [14]	123.6	92.2	45	99.9	103.5	45	13.8%	0.24 [-0.18, 0.65]	2012
Alshayeb et al. (ESRD) [11]	2,306	2,664	14	2,137	2,632	14	6.5%	0.06 [-0.68, 0.80]	2014
Alshayeb et al. (normal GFR) [11]	119.9	37.7	25	74.9	32.3	25	8.6%	1.26 [0.65, 1.87]	2014
Nygaard et al. [16]	43.5	10.5	22	39.5	9	22	8.9%	0.40 [-0.20, 1.00]	2014
Alshayeb et al. (CKD) [11]	191.1	116.9	27	169.7	110	27	10.3%	0.19 [-0.35, 0.72]	2014
Kamelian et al. [15]	111.9	229	60	99.6	71.9	60	15.9%	0.07 [-0.29, 0.43]	2017
Carvalho et al. [12]	1,470	3,718.6	16	1,360	2,782.2	16	7.2%	0.03 [-0.66, 0.73]	2017
Turrini et al. [17]	44.2	26.4	17	32.2	25.6	17	7.3%	0.45 [-0.23, 1.13]	2017
De Niet et al. (monthly) [13]	63.6	14.3	30	57.3	16.3	30	10.9%	0.41 [-0.11, 0.92]	2018
De Niet et al. (daily) [13]	63	18.8	30	51.9	16.4	30	10.7%	0.62 [0.10, 1.14]	2018
Total (95% CI)			**286**			**286**	**100.0%**	**0.36 [0.14, 0.57]**	

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 14.06$, df = 9 (P = 0.12); $I^2 = 36\%$

Test for overall effect: Z = 3.27 (P = 0.001)

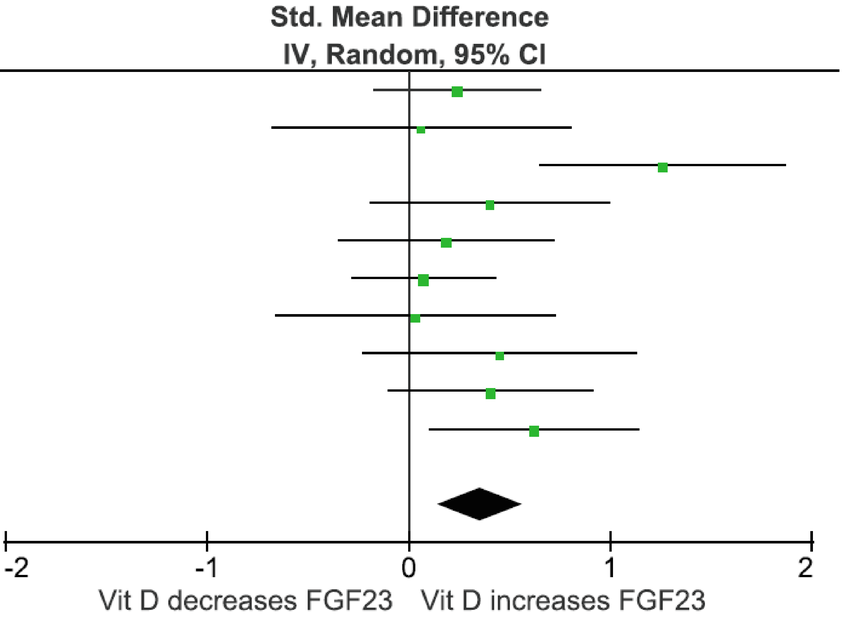
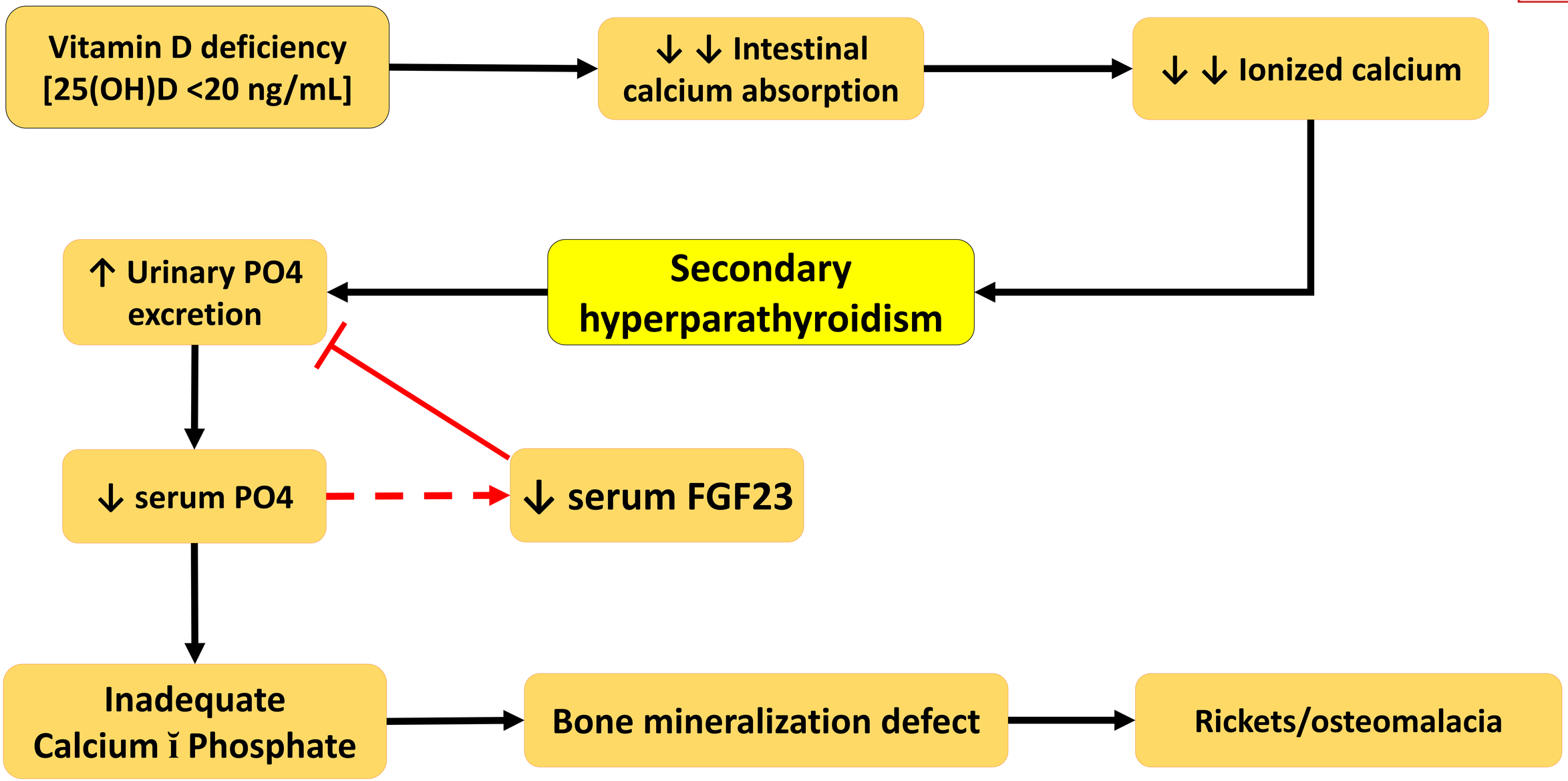
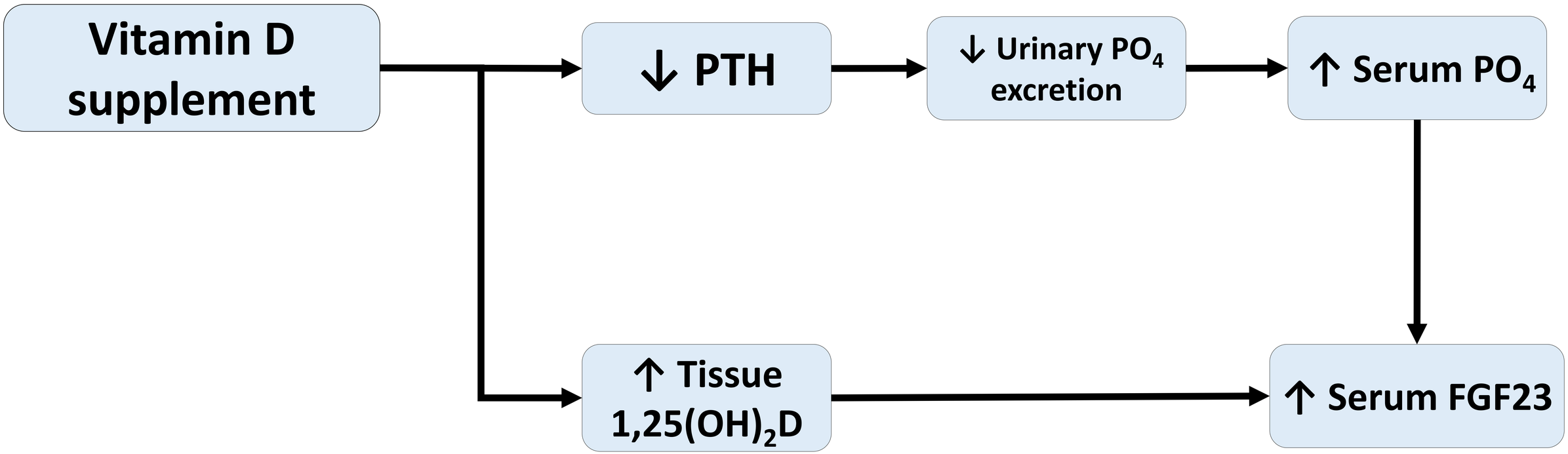


Fig. 2 Forest plot of the meta-analysis of change in serum intact FGF23 concentration after oral vitamin D_3 supplementation in vitamin D-deficient patients

Oral vitamin D_3 supplementation increases serum fibroblast growth factor 23 concentration in vitamin D-deficient patients: a systematic review and meta-analysis



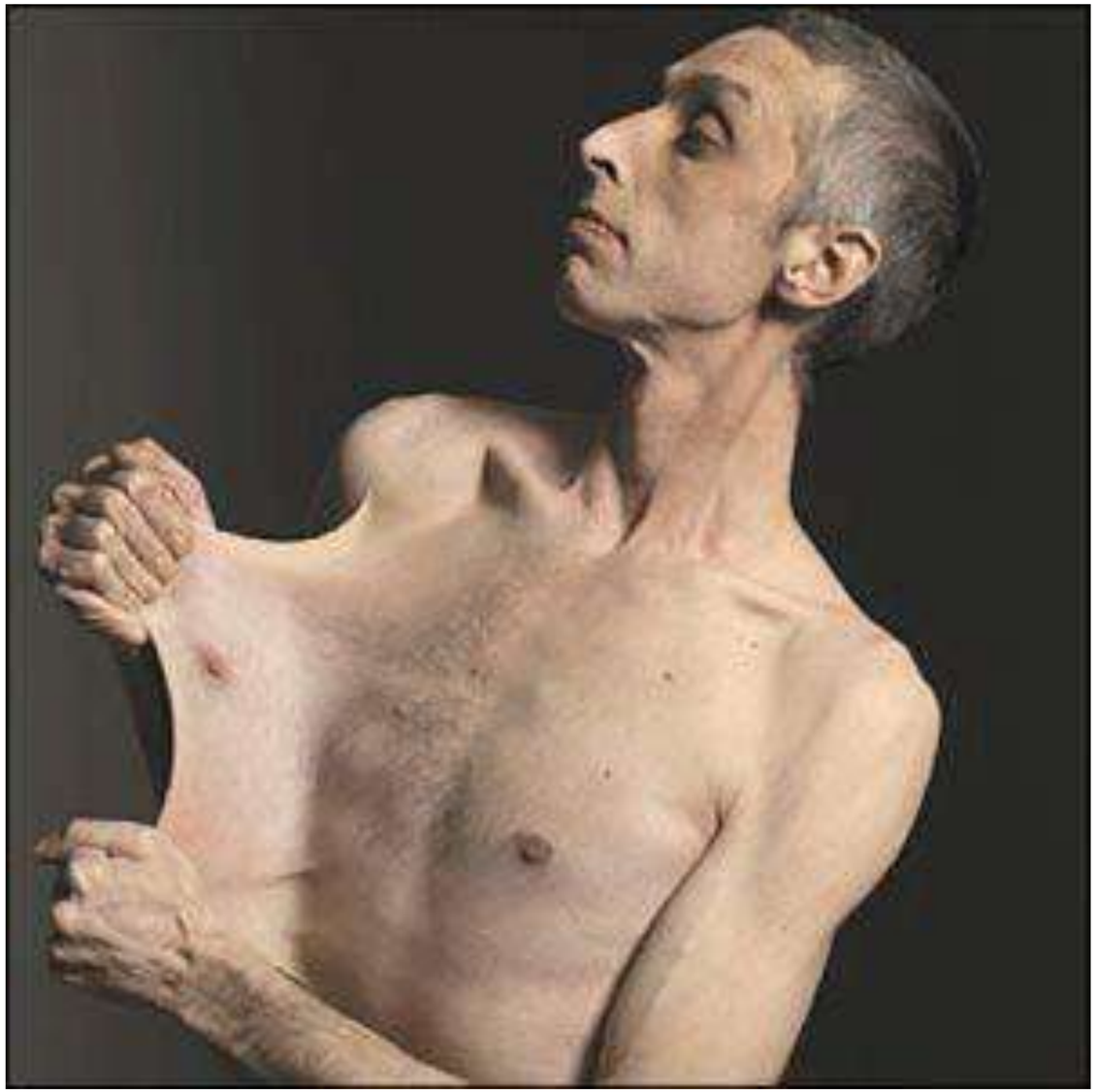
Oral vitamin D_3 supplementation increases serum fibroblast growth factor 23 concentration in vitamin D-deficient patients: a systematic review and meta-analysis



Whole Genome Sequencing for Determining the Causative Genetic Variations in Patients with Ehlers–Danlos Syndrome

Arash Shirvani, Nipith Charoenngam, Tyler A. Kalajian, Grace H. Yoon, Nickie St Clair, Michael F. Holick
Section Endocrinology, Diabetes, Nutrition and Weight Management, Department of Medicine, Boston University School of Medicine

Ehlers-Danlos Syndrome



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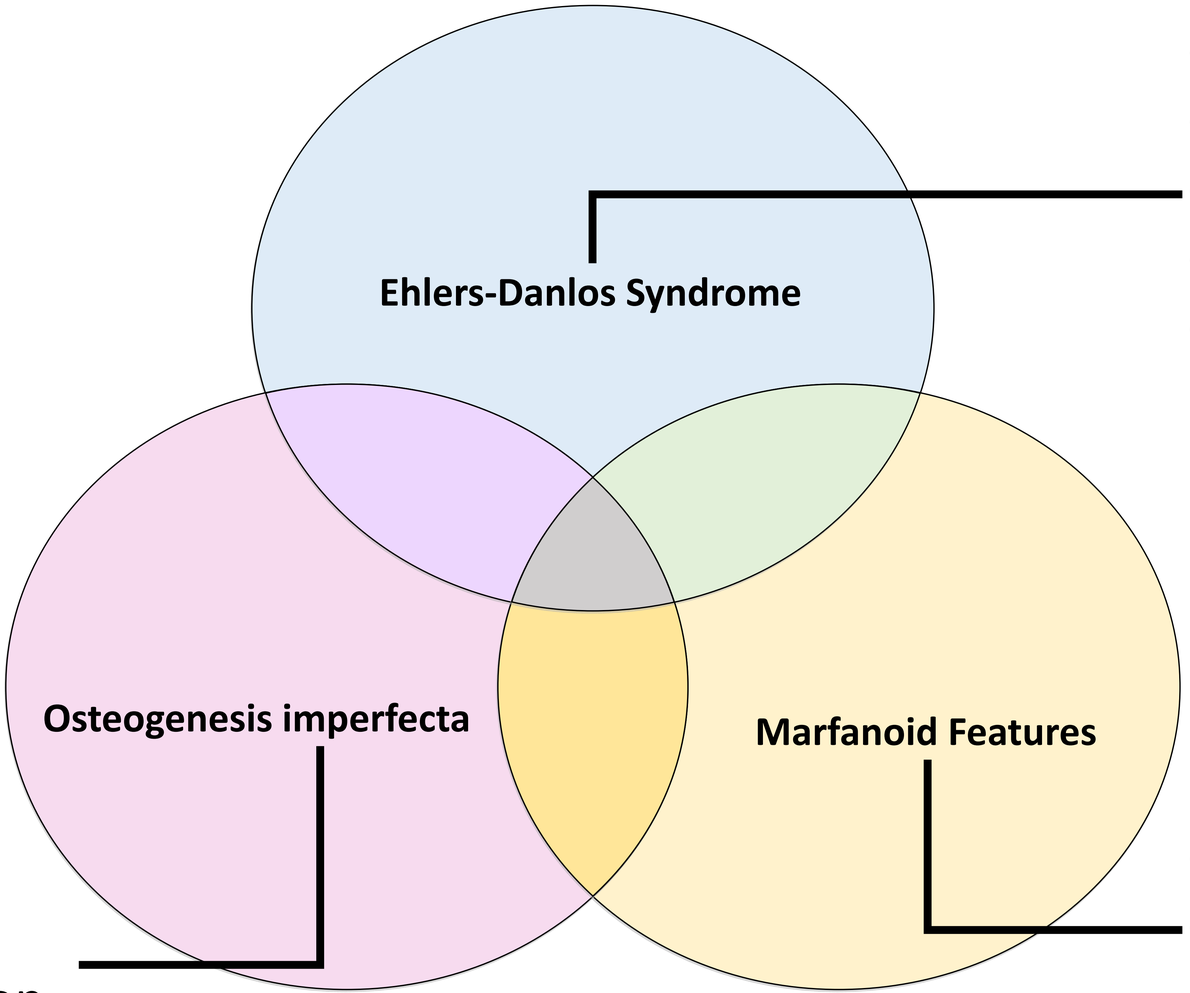
Connective tissue disorders



- Joint hypermobility
- Skin hyperextensibility
- Mast cell hypersensitivity
- Vascular fragility
- Delayed wound healing
- Dysautonomia

  etc.

- Bone fragility
- Scleral discoloration

- Increased arm span/height
- Long fingers
- Long face

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Ehlers-Danlos Syndrome

Name of EDS Subtype	*IP**	*Genetic Basis*	*Protein Involved*
Classical EDS (cEDS)	AD	Major: *COL5A1, COL5A2*	Type V collagen
		Rare: *COL1A1* c.934C>T, p.(Arg312Cys)	Type I collagen
Classical-like EDS (clEDS)	AR	*TNXB*	Tenascin XB
Cardiac-valvular EDS (cvEDS)	AR	*COL1A2* (biallelic mutations that lead to *COL1A2* NMD and absence of pro ▫2(I) collagen chains)	Type I collagen
Vascular EDS (vEDS)	AD	Major: *COL3A1*	Type III collagen
		Rare: *COL1A1* c.934C>T, p.(Arg312Cys) c.1720C>T, p.(Arg574Cys) c.3227C>T, p.(Arg1093Cys)	Type I collagen
Hypermobile EDS (hEDS)	AD	Unknown	Unknown
Arthrochalasia EDS (aEDS)	AD	*COL1A1, COL1A2*	Type I collagen
Dermatosparaxis EDS (dEDS)	AR	*ADAMTS2*	ADAMTS-2
Kyphoscoliotic EDS (kEDS)	AR	*PLOD1*	LH1
		FKBP14	FKBP22
Brittle cornea syndrome (BCS)	AR	*ZNF469*	ZNF469
		PRDM5	PRDM5
Spondylodysplastic EDS (spEDS)	AR	*B4GALT7*	ß4GalT7
		B3GALT6	ß3GalT6
		SLC39A13	ZIP13
Musculocontractural EDS (mcEDS)	AR	*CHST14*	D4ST1
		DSE	DSE
Myopathic EDS (mEDS)	AD or AR	*COL12A1*	Type XII collagen
Periodontal EDS (pEDS)	AD	*C1R*	C1r

The Ehlers Danlos Society

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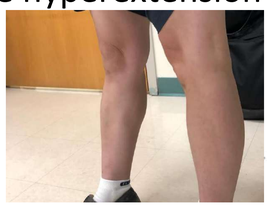
Ehlers-Danlos Syndrome

The Beighton score

Assessment site	Right	Left	Assessment site	Right	Left
Elbow hyperextension >10° 	1 point	1 point	Hyperextension of 5th MCP 	1 point	1 point
Thumb touching the forearm 	1 point	1 point	Knee hyperextension >10° 	1 point	1 point
Forward flexion of trunk, leg straight, palm touching floor 	1 point		**Total**	**9 points**	

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Ehlers-Danlos Syndrome Clinical Research Program

Aim

- To determine causative genetic variations responsible for a variety of clinical manifestations of EDS patients

What we have achieved so far

- DNA biobank and clinical data of 310 patients from 80 families with 2 – 4 generations
- A pilot WGS from index cases revealing genetic variations in TNXB gene which has been previously reported to be associated with EDS and several other novel genetic variations

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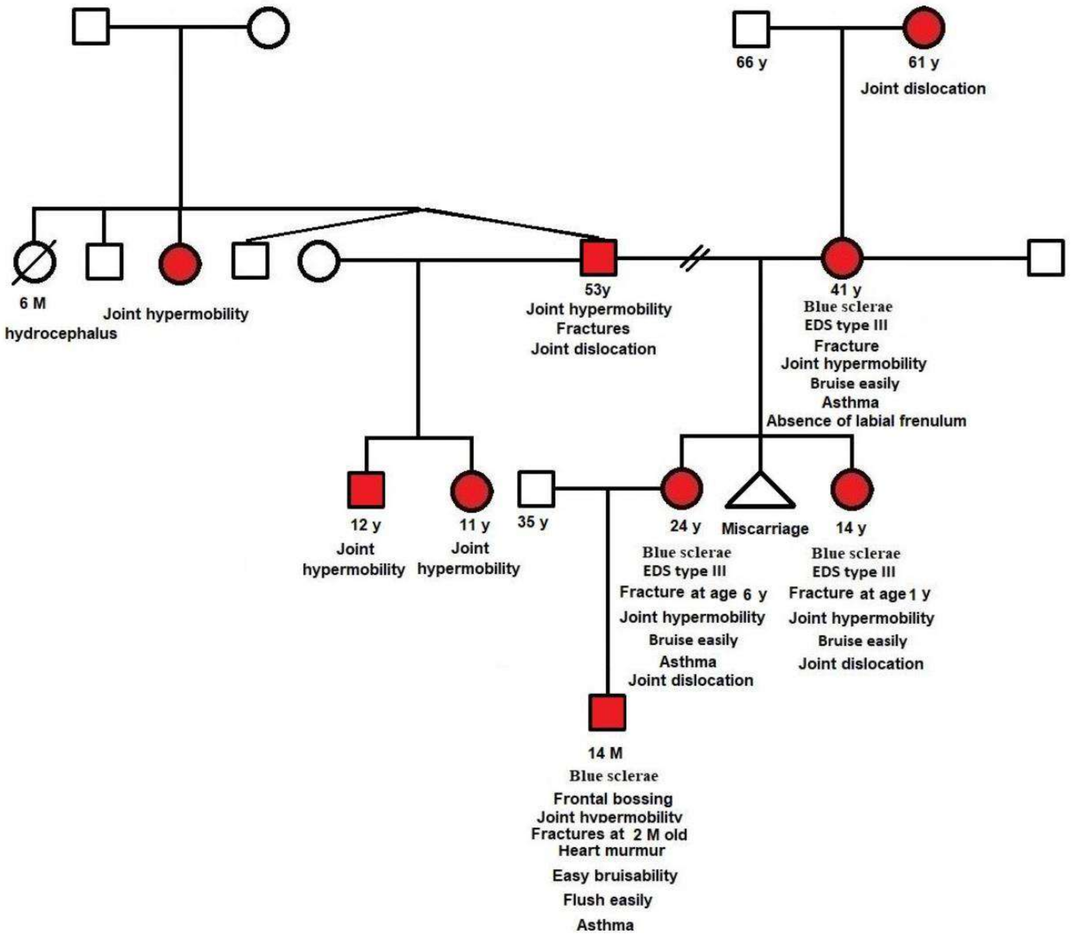
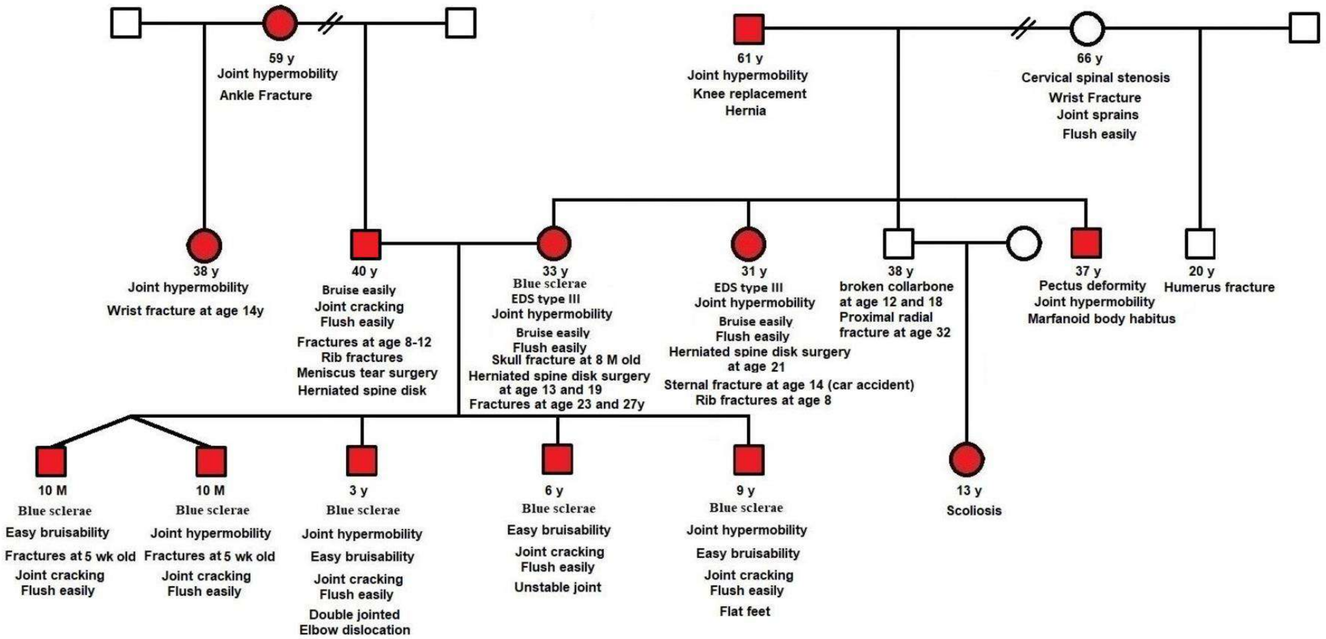
Ehlers-Danlos Syndrome Clinical Research Program





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Reviews

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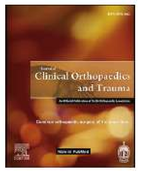

Vitamin D for skeletal and non-skeletal health: What we should know

Nipith Charoenngam [a, b, *], Arash Shirvani [a], Michael F. Holick [a]

[a] Department of Medicine, Section of Endocrinology, Nutrition, and Diabetes, Vitamin D, Skin and Bone Research Laboratory, Boston University Medical Center, Boston, MA, USA
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ABSTRACT

Vitamin D plays an essential role in regulating calcium and phosphate metabolism and maintaining a healthy mineralized skeleton. Humans obtain vitamin D from sunlight exposure, dietary foods and supplements. There are two forms of vitamin D: vitamin D_3 and vitamin D_2. Vitamin D_3 is synthesized endogenously in the skin and found naturally in oily fish and cod liver oil. Vitamin D_2 is synthesized from ergosterol and found in yeast and mushrooms. Once vitamin D enters the circulation it is converted by 25-hydroxylase in the liver to 25-hydroxyvitamin D [25(OH)D], which is further converted by the 25-hydroxyvitamin D-1α-hydroxylase in the kidneys to the active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. $1,25(OH)_2D$ binds to its nuclear vitamin D receptor to exert its physiologic functions. These functions include: promotion of intestinal calcium and phosphate absorption, renal tubular calcium reabsorption, and calcium mobilization from bone. The Endocrine Society's Clinical Practice Guideline defines vitamin D deficiency, insufficiency, and sufficiency as serum concentrations of 25(OH)D of <20 ng/mL, 21–29 ng/mL, and 30–100 ng/mL, respectively. Vitamin D deficiency is a major global public health problem in all age groups. It is estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency. This pandemic of vitamin D deficiency and insufficiency is attributed to a modern lifestyle and environmental factors that restrict sunlight exposure, which is essential for endogenous synthesis of vitamin D in the skin. Vitamin D deficiency is the most common cause of rickets and osteomalacia, and can exacerbate osteoporosis. It is also associated with chronic musculoskeletal pain, muscle weakness, and an increased risk of falling. In addition, several observational studies observed the association between robust levels of serum 25(OH)D in the range of 40–60 ng/mL with decreased mortality and risk of development of several types of chronic diseases. Therefore, vitamin D-deficient patients should be treated with vitamin D_2 or vitamin D_3 supplementation to achieve an optimal level of serum 25(OH)D. Screening of vitamin D deficiency by measuring serum 25(OH)D is recommended in individuals at risk such as patients with diseases affecting vitamin D metabolism and absorption, osteoporosis, and older adults with a history of falls or nontraumatic fracture. It is important to know if a laboratory assay measures total 25(OH)D or only $25(OH)D_3$. Using assays that measure only $25(OH)D_3$ could underestimate total levels of 25(OH)D and may mislead physicians who treat patients with vitamin D_2 supplementation.

Reviews

REVIEW

The ongoing D-lemma of vitamin D supplementation for nonskeletal health and bone health

Nipith Charoenngam[a,b], *Arash Shirvani*[a], *and Michael F. Holick*[a]

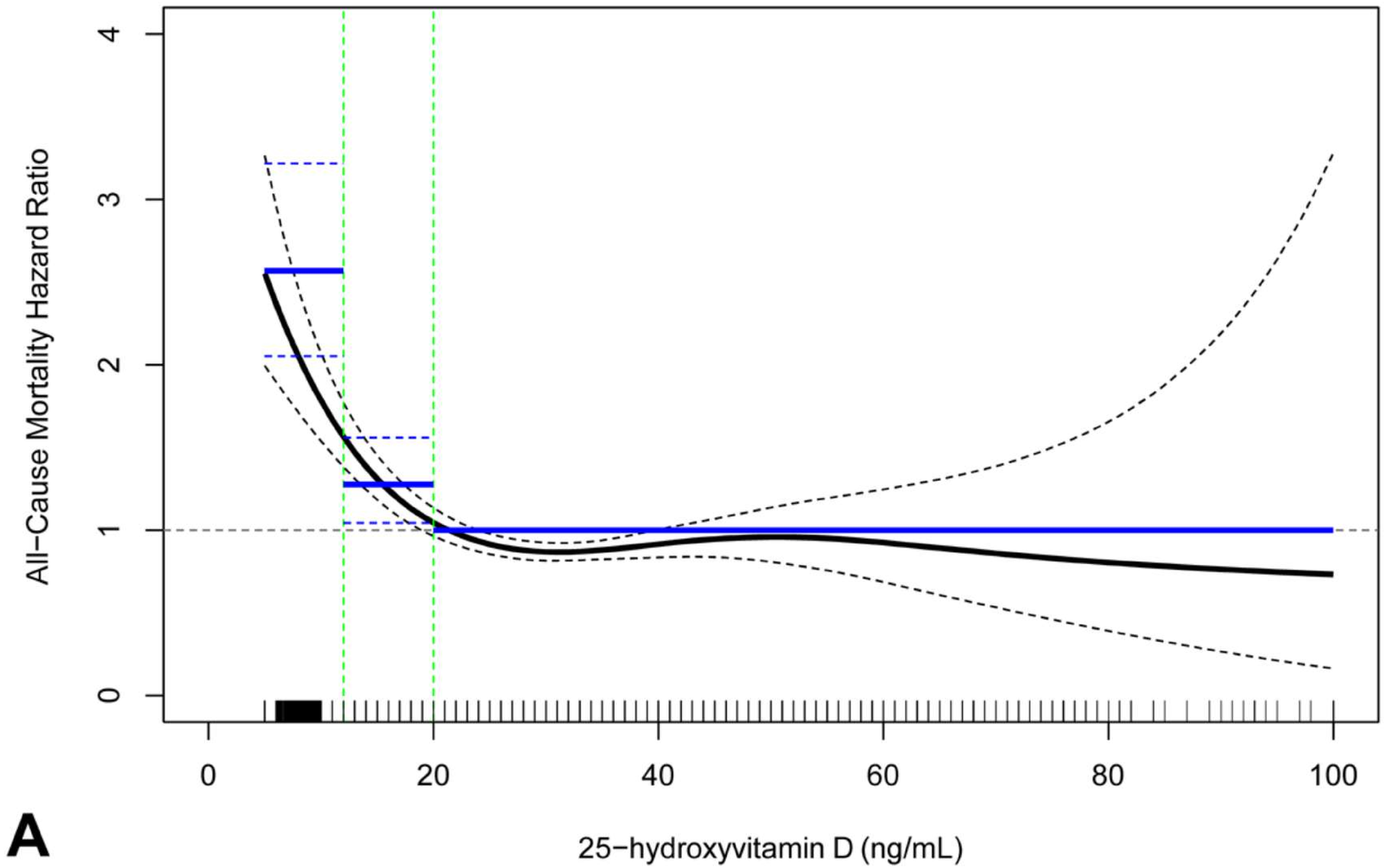
Purpose of review
The goal of this review is to give some perspective on the results and conclusions of three recent randomized controlled vitamin D intervention studies that have challenged the health benefit of vitamin D supplementation for reducing risk for cardiovascular disease, cancer, all-cause mortality and type 2 diabetes and improving bone health.

Recent findings
Vitamin D supplementation to adults who were vitamin D sufficient or insufficient did not reduce risk for developing cardiovascular disease, cancer, type 2 diabetes nor increases bone mineral density (BMD). Patients who were vitamin D deficient with cancer and received vitamin D reduced risk for mortality by 25% and prediabetic adults who were vitamin D deficient and received vitamin D reduced their risk of developing type 2 diabetes by 62%. Older adults receiving 4000 and 10 000 IUs of vitamin D_3 daily for 3 years had reduced radial BMD but had no change in either total hip areal bone density or bone strength in the radius and tibia.

Summary
Caution is needed when evaluating results and conclusions from randomized controlled trials that investigate health benefits of vitamin D; most studies suggest health benefits when vitamin D supplementation is provided to vitamin D deficient populations and little benefit when given to populations that are vitamin D sufficient/insufficient.

Keywords
25-hydroxyvitamin D, bone health, D2d, VITAL, vitamin D

Vitamin D and mortality



Dudenkov DV Mayo Clin Proc. 2018;93(6):721–730.

BOSTON UNIVERSITY SCHOOL of Medicine

VITAL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., Vadim Bubes, Ph.D., Edward L. Giovannucci, M.D., Sc.D., Walter C. Willett, M.D., Dr.P.H., and Julie E. Buring, Sc.D., for the VITAL Research Group*

2,000 IUs Vitamin D_3 daily for 5 years

CONCLUSIONS

Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, NCT01169259.)

D2d

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vitamin D Supplementation and Prevention of Type 2 Diabetes

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4,000 IUs Vitamin D_3 daily for 3 years

CONCLUSIONS

Among persons at high risk for type 2 diabetes not selected for vitamin D insufficiency, vitamin D_3 supplementation at a dose of 4000 IU per day did not result in a significantly lower risk of diabetes than placebo. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; D2d ClinicalTrials.gov number, NCT01942694.)

VITAL

Table 2. Hazard Ratios and 95% Confidence Intervals for the Primary, Secondary, and Other End Points, According to Randomized Assignment to Vitamin D or Placebo, in Intention-To-Treat Analyses.*

End Point	Vitamin D Group (N = 12,927)	Placebo Group (N = 12,944)	Hazard Ratio (95% CI)
	no. of participants with event		
Analyses excluding the first 2 yr of follow-up			
Invasive cancer of any type	490	522	0.94 (0.83–1.06)
Death from cancer	112	149	0.75 (0.59–0.96)
Major cardiovascular event	274	296	0.93 (0.79–1.09)
Death from any cause	368	384	0.96 (0.84–1.11)

Baseline serum 25-hydroxyvitamin D	15,787
<20 ng/ml	2,001
≥20 ng/ml	13,786
Baseline vitamin D use‡	25,871
Yes	11,030
No	14,841

D2d

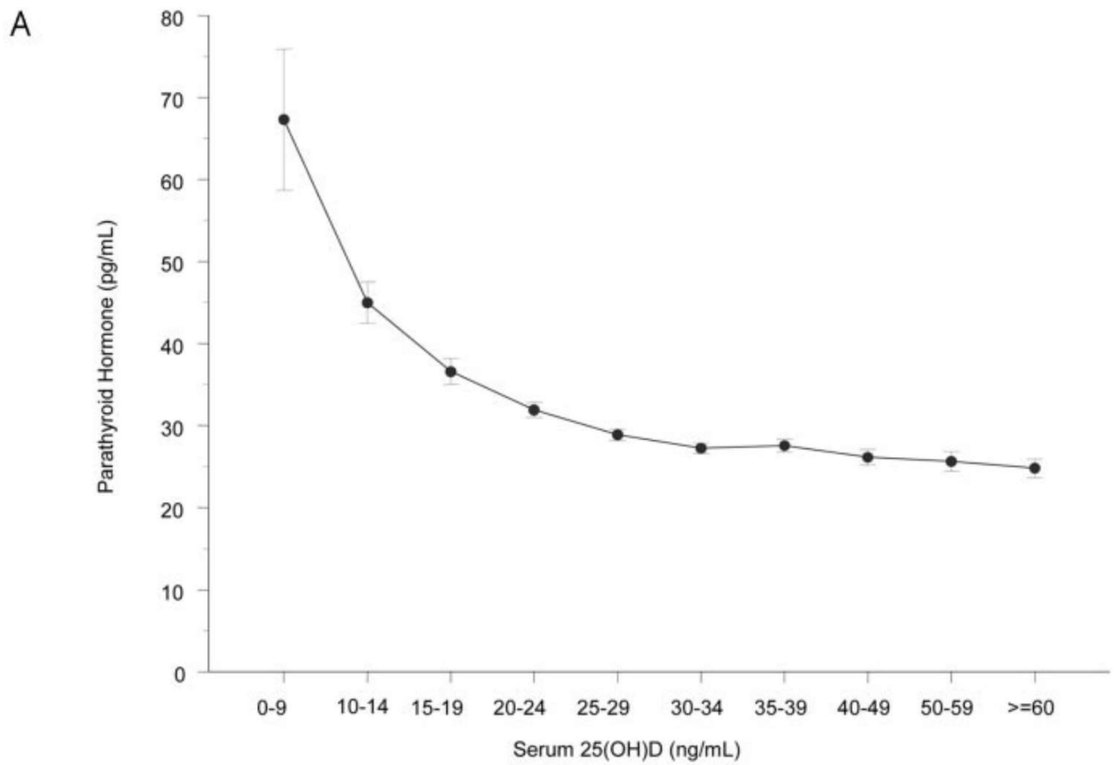
In a post hoc analysis of data from participants with a baseline 25-hydroxyvitamin D level of less than 12 ng per milliliter (30 nmol per liter) (103 participants), the hazard ratio in the vitamin D group was 0.38 (95% CI, 0.18 to 0.80). Among those with a baseline 25-hydroxyvitamin D level equal to or greater than 12 ng per milliliter (2319 participants), the hazard ratio in the vitamin D group was 0.92 (95% CI, 0.78 to 1.08).

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Overall (N = 2423)	Vitamin D (N = 1211)	Placebo (N = 1212)
Serum 25-hydroxyvitamin D			
Mean — ng/ml	28.0±10.2	27.7±10.2	28.2±10.1
Distribution — no./total no. (%)‡			
<12 ng/ml	103/2422 (4.3)	60/1211 (5.0)	43/1211 (3.6)
12–19 ng/ml	422/2422 (17.4)	216/1211 (17.8)	206/1211 (17.0)
20–29 ng/ml	876/2422 (36.2)	453/1211 (37.4)	423/1211 (34.9)
≥30 ng/ml	1021/2422 (42.2)	482/1211 (39.8)	539/1211 (44.5)

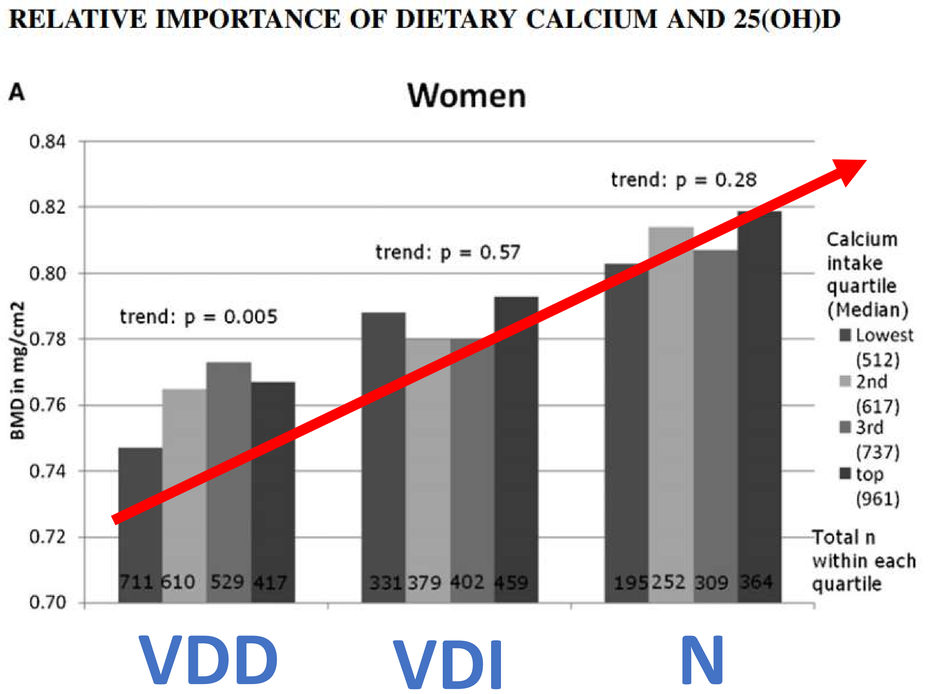
Vitamin D and bone health

Serum PTH

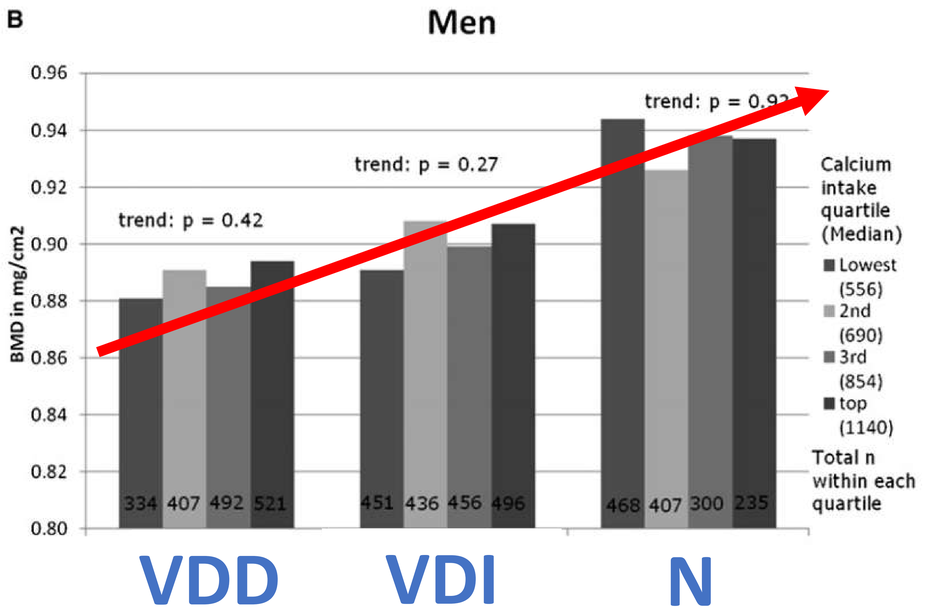


Serum 25(OH)D

BMD



BMD



Holick et al. J Clin Endocrinol Metab 90: 3215–3224, 2005

Bischoff-Ferrari HA et al. J Bone Miner Res. 2009;24(5):935-942.

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Research

JAMA | Original Investigation

Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength
A Randomized Clinical Trial

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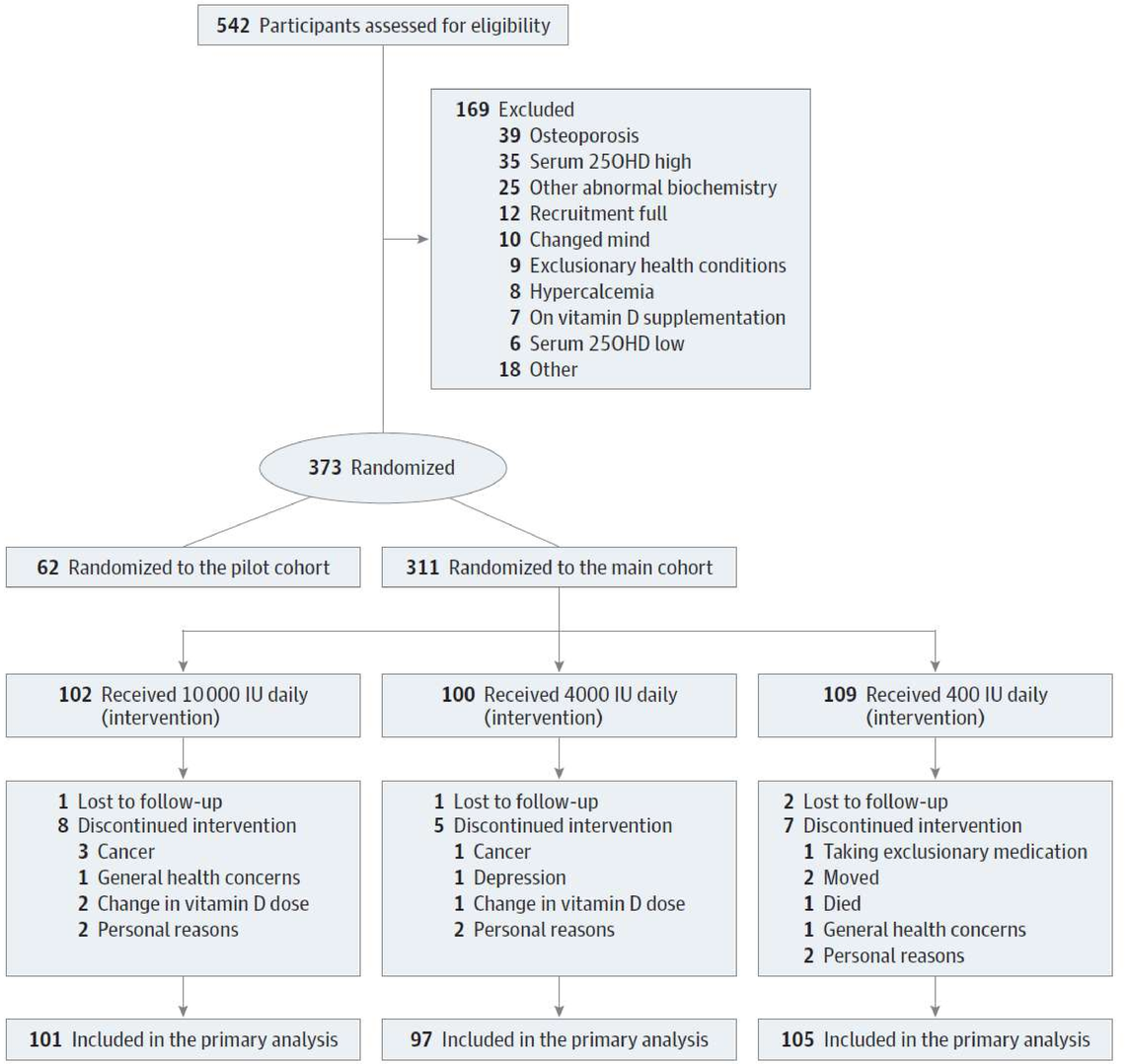
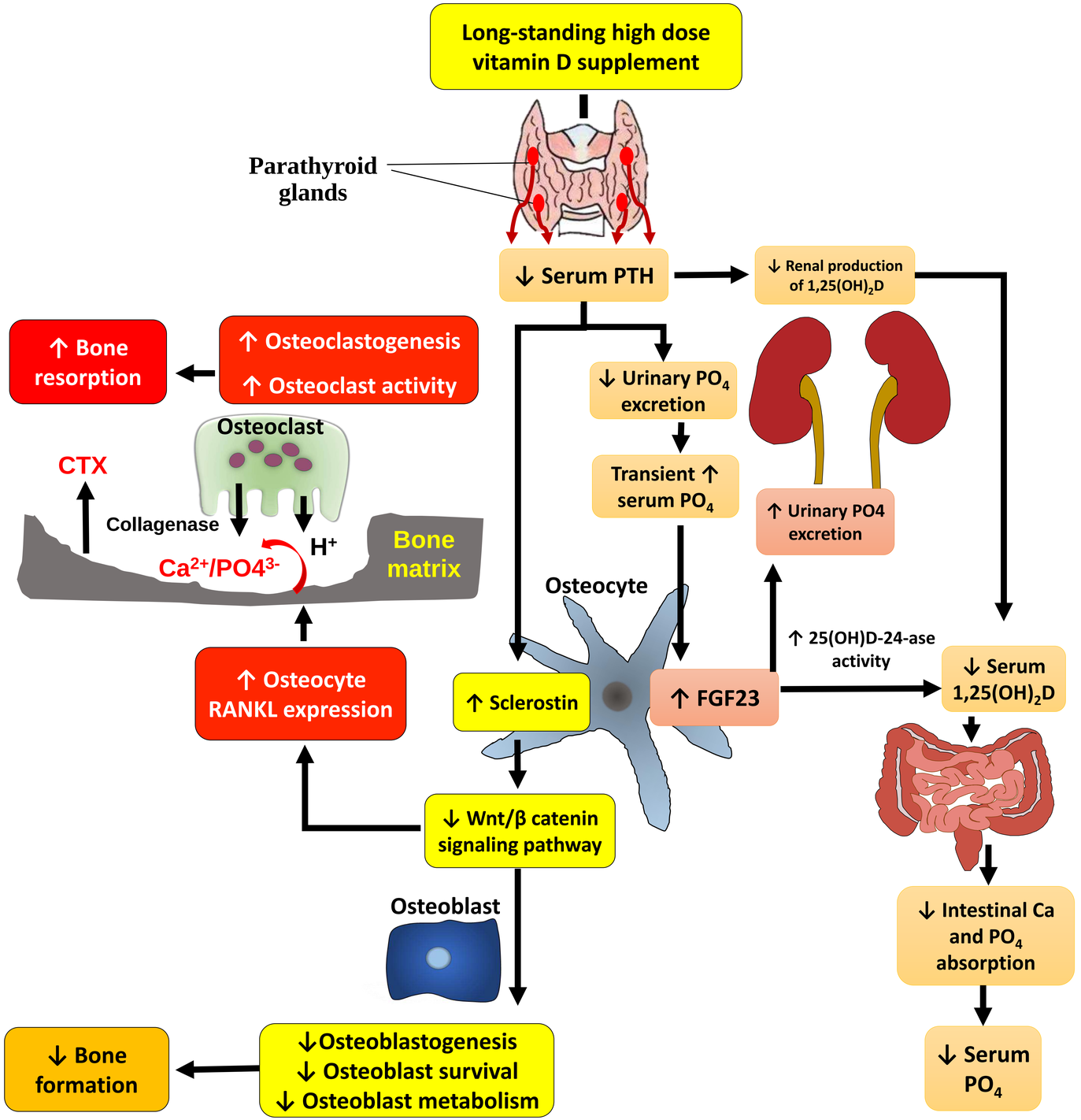
Figure 1. Flow Diagram of Participants Through the Study



CONCLUSIONS AND RELEVANCE Among healthy adults, treatment with vitamin D for 3 years at a dose of 4000 IU per day or 10 000 IU per day, compared with 400 IU per day, resulted in statistically significant lower radial BMD; tibial BMD was significantly lower only with the 10 000 IU per day dose. There were no significant differences in bone strength at either the radius or tibia. These findings do not support a benefit of high-dose vitamin D supplementation for bone health; further research would be needed to determine whether it is harmful.

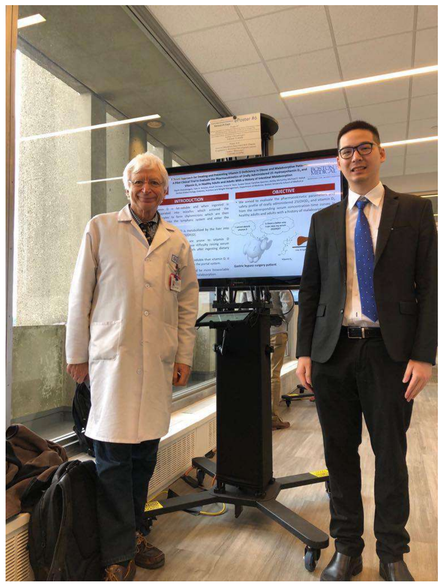
Table 1. Baseline Demographic, Health Characteristics, and Laboratory Values

	No. (%)		
Variable	10 000 IU	4000 IU	400 IU
No. of participants	101	97	105
Laboratory values			
Serum			
25(OH)D, nmol/L	78.4 (18.4)	81.3 (20.1)	76.7 (21.0)


Long-standing high dose vitamin D supplement
Parathyroid glands
↓ Serum PTH
↓ Renal production of 1,25(OH)2D
↑ Bone resorption
↑ Osteoclastogenesis
↑ Osteoclast activity
Osteoclast
CTX
Collagenase
H+
Ca2+/PO43-
Bone matrix
↓ Urinary PO4 excretion
Transient ↑ serum PO4
↑ Urinary PO4 excretion
Osteocyte
↑ 25(OH)D-24-ase activity
↑ Osteocyte RANKL expression
↑ Sclerostin
↑ FGF23
↓ Serum 1,25(OH)2D
↓ Wnt/β catenin signaling pathway
Osteoblast
↓ Intestinal Ca and PO4 absorption
↓ Bone formation
↓Osteoblastogenesis
↓ Osteoblast survival
↓ Osteoblast metabolism
↓ Serum PO4

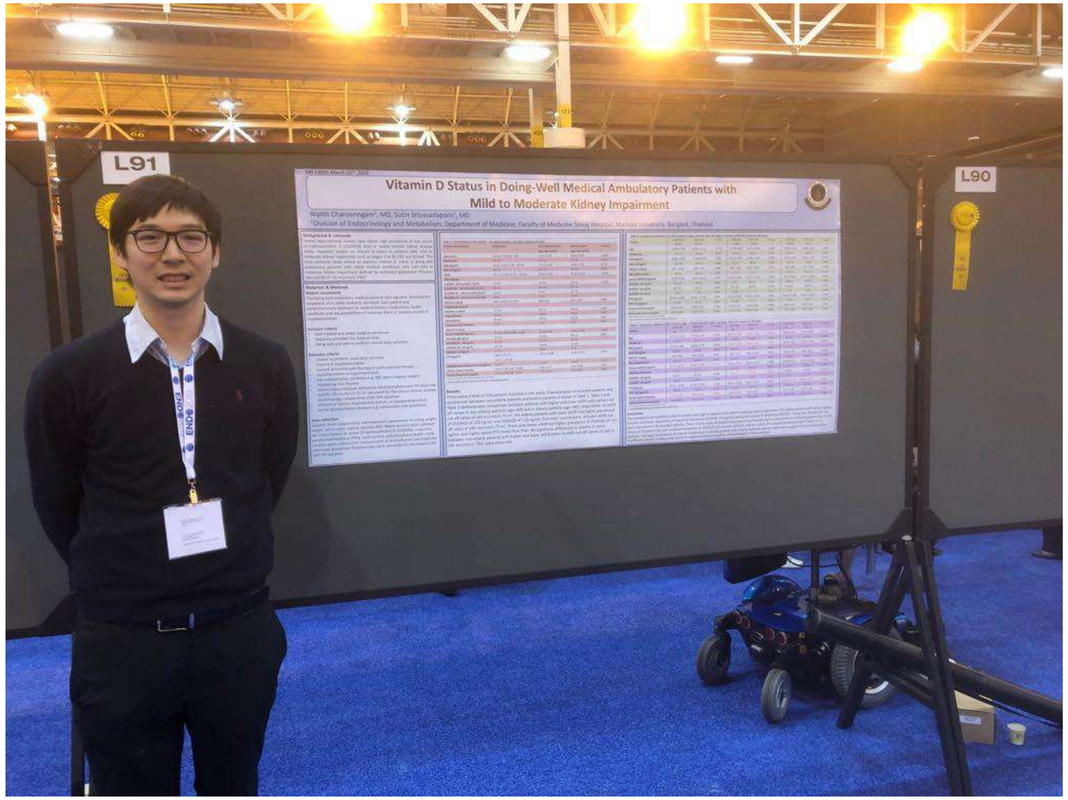
Research presentation

Oral-Blitz presentation BUSM



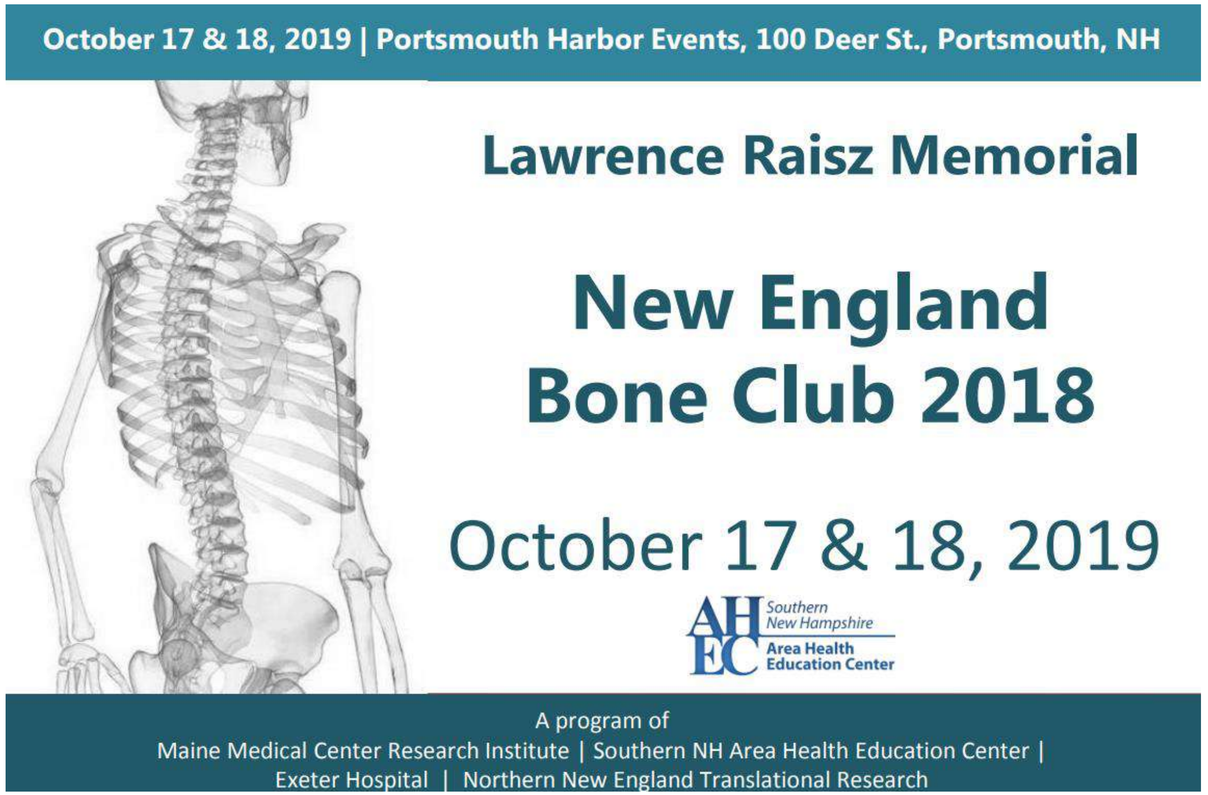
Poster presentation BUSM

Research presentation



Poster presentation ENDO 2019

Research presentation

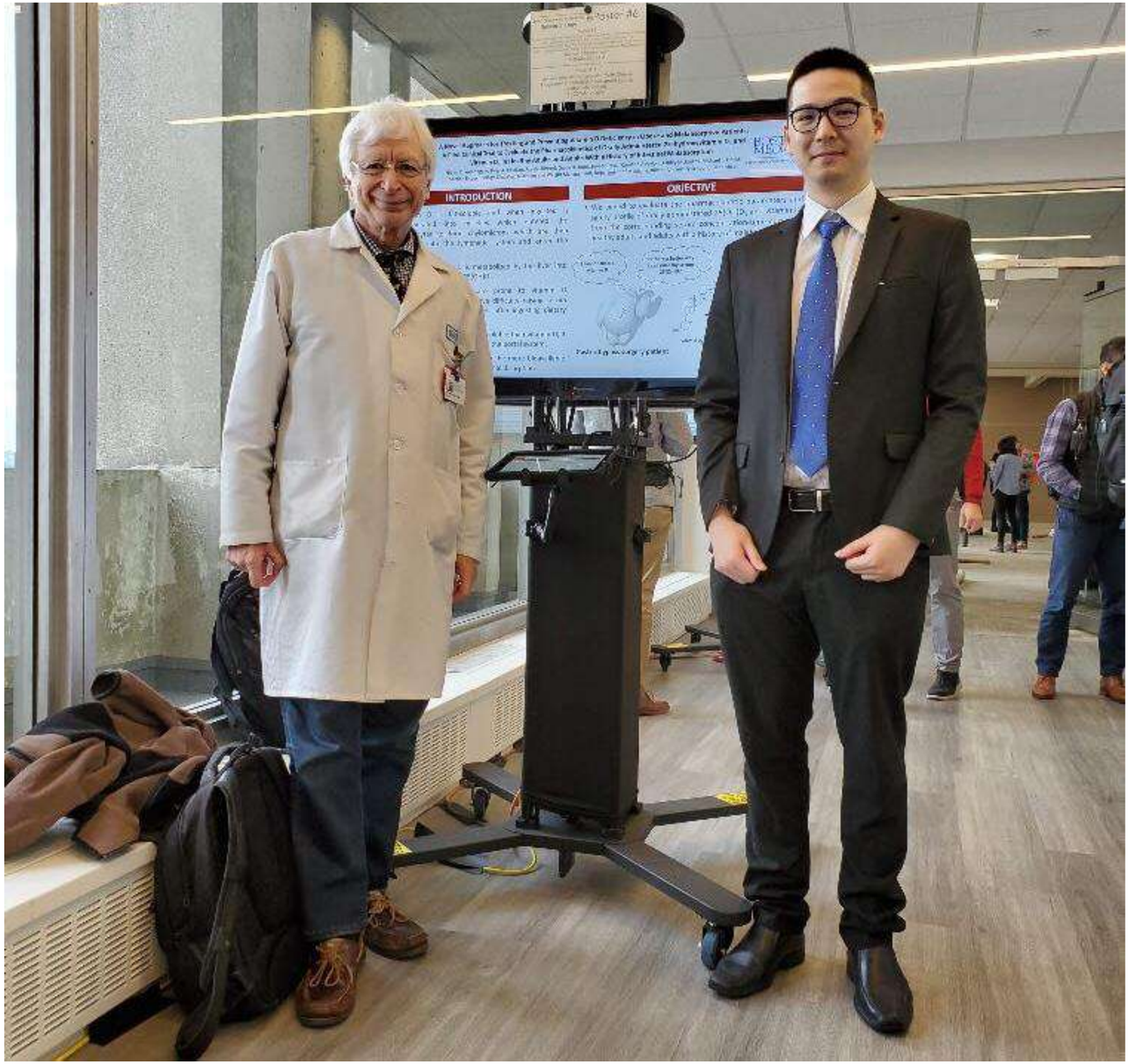


Oral presentation NE Bone club 2019

My Siriraj Mentors


SMO Tx


General Clinical Research Center


INTRODUCTION
OBJECTIVE

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THANK YOU