Vitamin D and its current relevance

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This meeting is sponsored and funded by Thornton and Ross Pharmaceuticals.
The views are those of the speaker.

Prescribing information can be found on the last slide.

This presentation includes a discussion of medical conditions which are outside of the licensed indication for Fultium®-D_3 (Colecalciferol)

The value of vitamin D supplements in these settings is unproven at the present time. Please refer to the Fultium-D_3 API for more information

Disclosure Statement

Speakers Name: Dr Bala Srinivasan, MD, FRCP (Glas)

I have the following potential conflicts of interest to report:

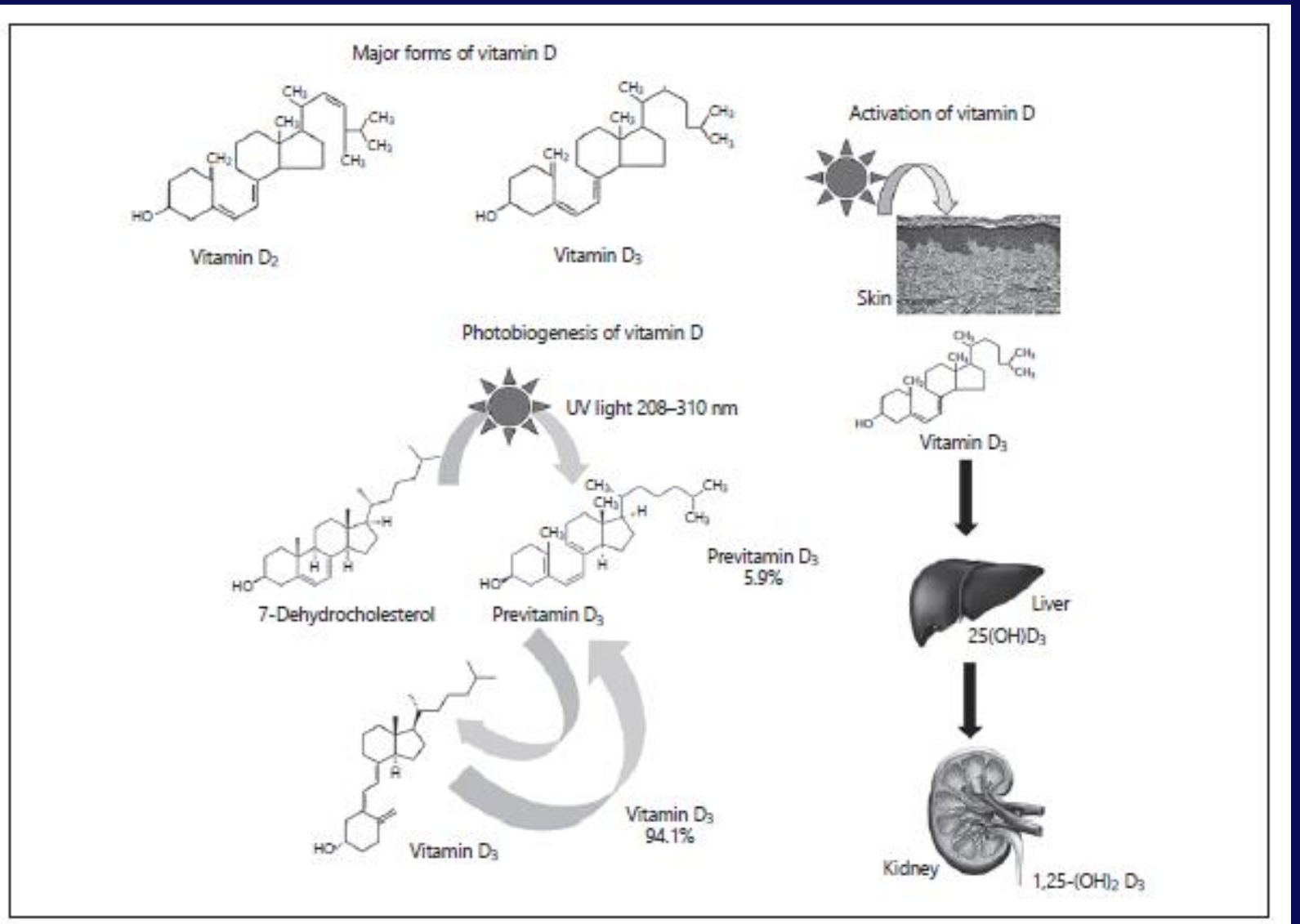
- **Research Contracts: Sanofi and MSD**
- **I have spoken on behalf of the following companies: MSD, BMS-AZ, Eli Lilly, Sanofi**
- **Travel Grants: GSK, Novo Nordisk, Eli Lilly, Astra Zeneca**

Other(s) – *funding to chair this meeting from Thornton & Ross*

Learning Objectives

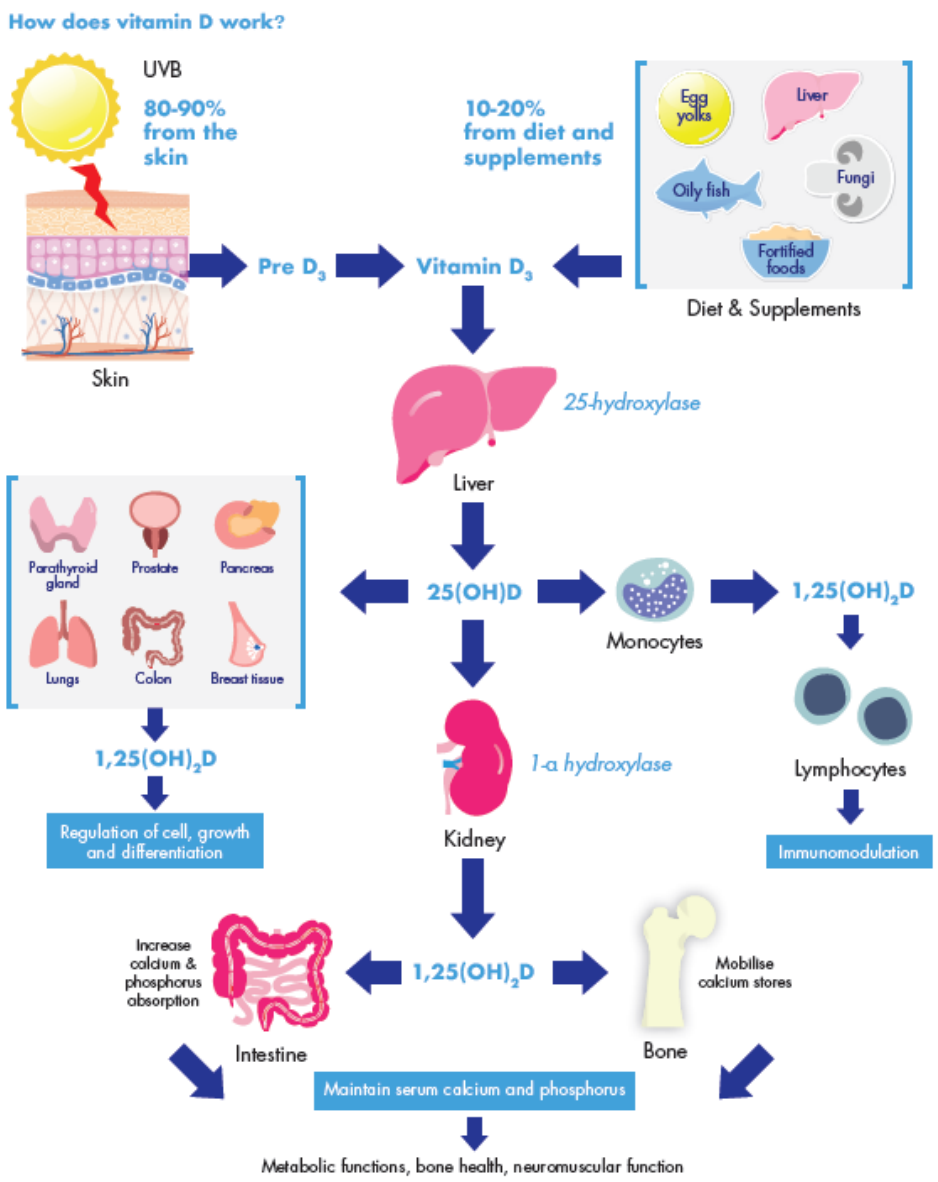
- Basic Physiology and role of Vitamin D
- Effect of Vitamin D on Bones
- Lesser known interesting effects
- Assess VDD
- Management
- COVID and Vitamin D

Vitamin D Metabolism



Ann Nutr Metab 2018;72:87–95

How is vitamin D metabolised?

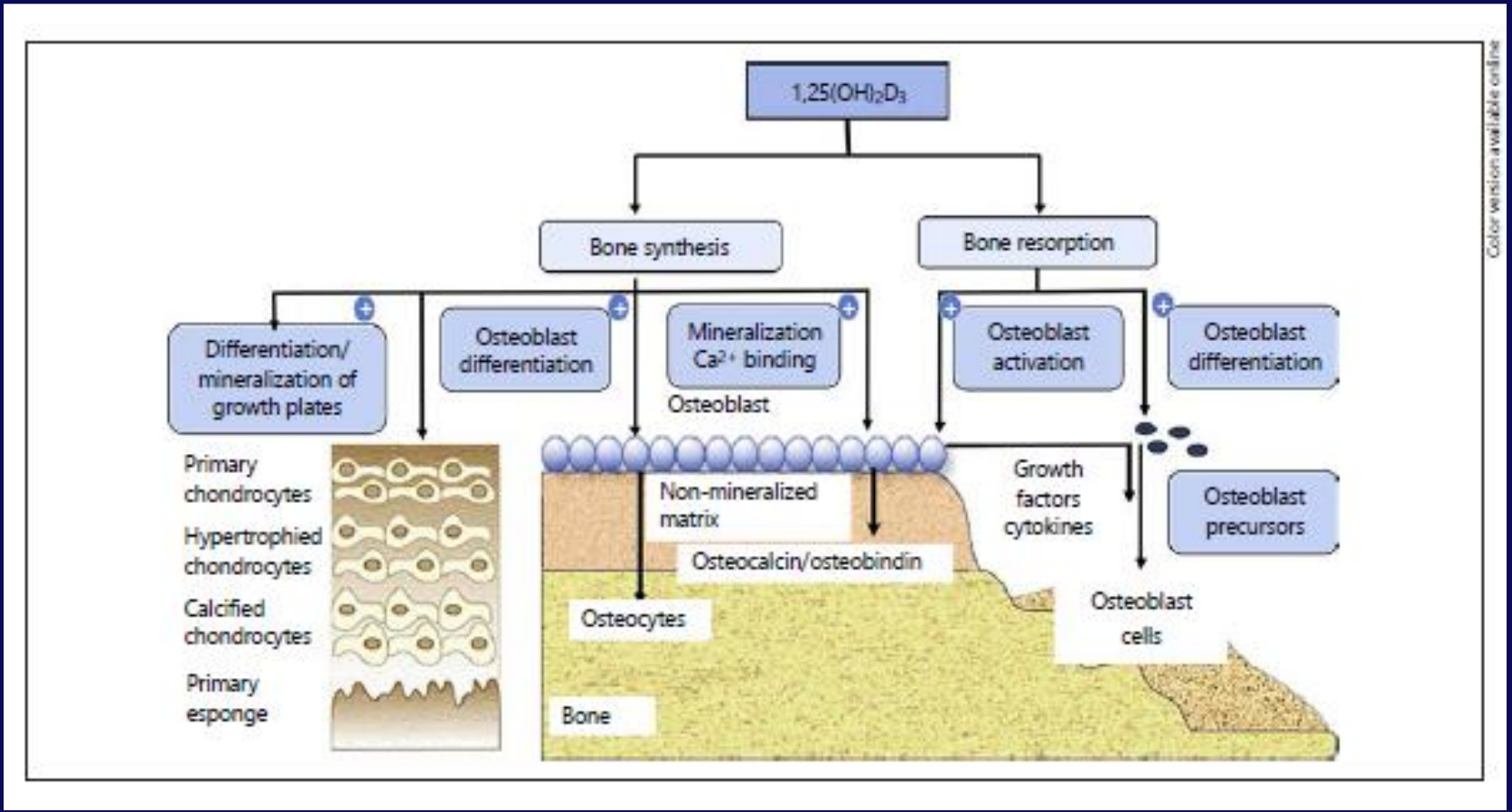


The backbone to vitamin D metabolism involves a two-step hydroxylation, first in the liver and then in the kidneys before becoming biologically active and useful for health.

These reactions are controlled by specific enzymes, are sensitive to circulatory concentrations of calcium and parathyroid hormone and are magnesium-dependent processes.

- Fraser WD and Milan AM. Vitamin D assays: past and present debates, difficulties, and developments *Calcified Tissue Intl* 2013; 92(2): 118-127
- Bikle D. Vitamin D metabolism, mechanisms of action and clinical applications. Chemistry and Biology Review; March 20, 2014. 319-329 https://www.sciencedirect.com/science/article/pii/S1074552114000246?via%3Dihub

Vitamin D and the Bone



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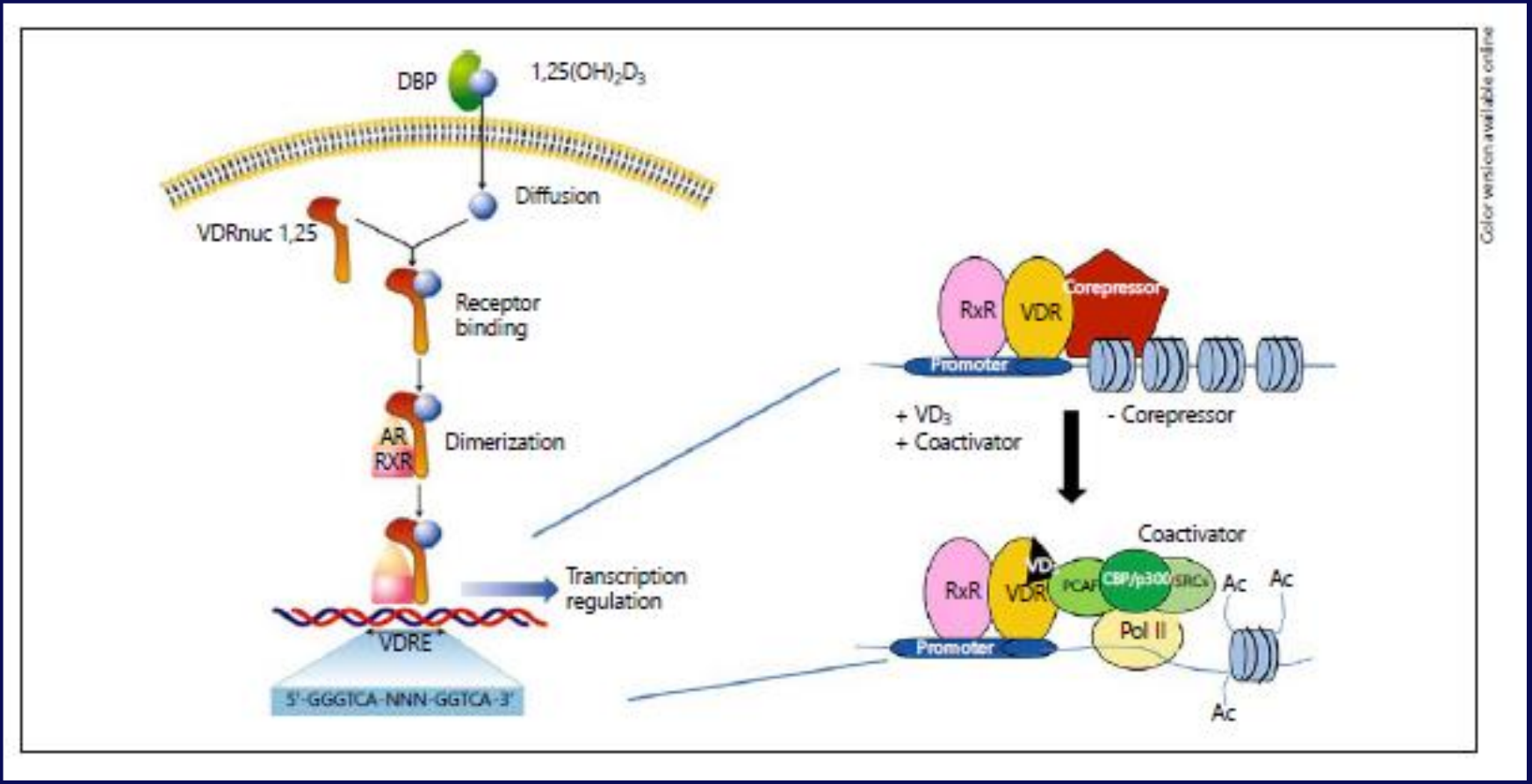
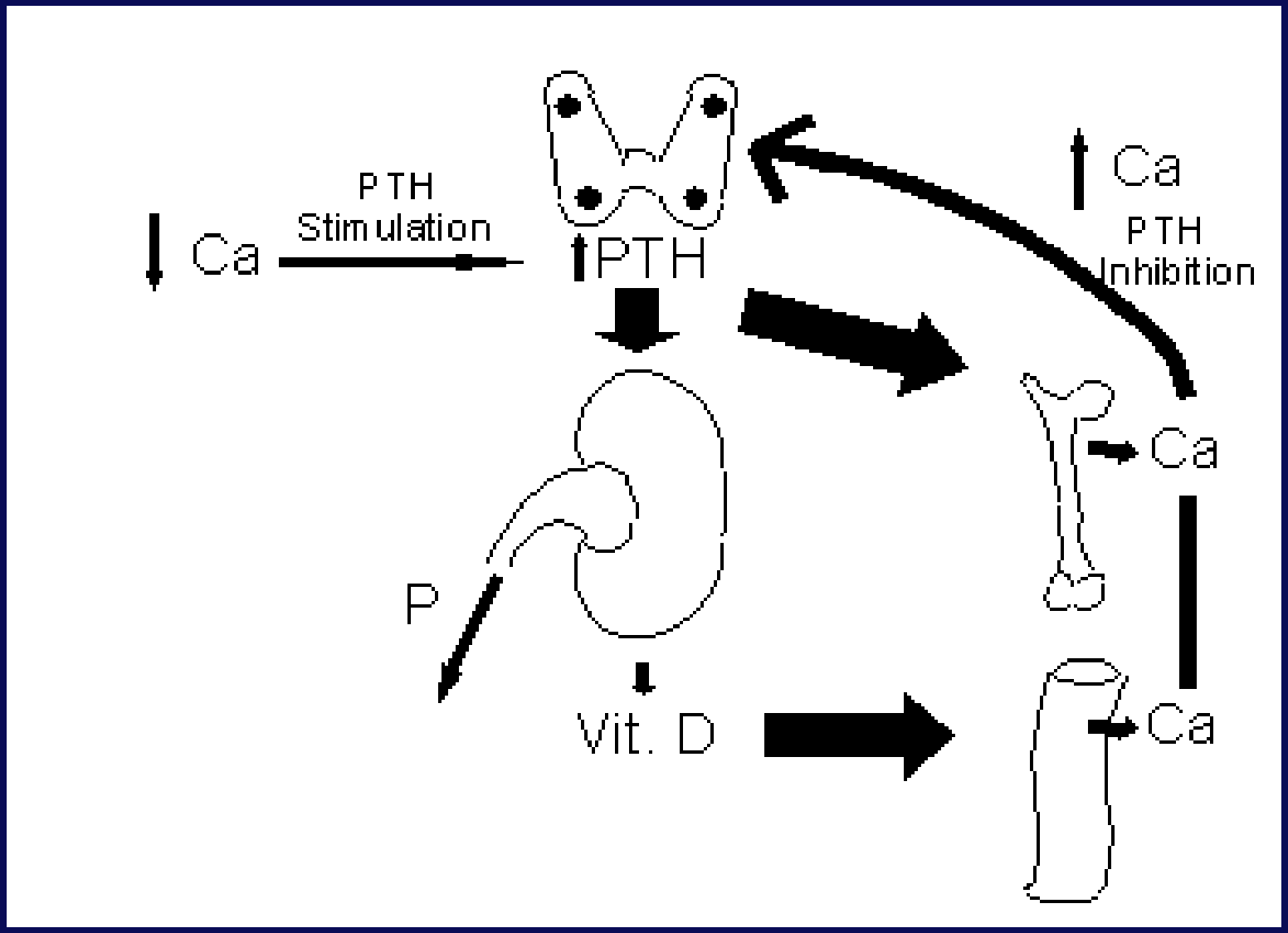
Molecular Mechanisms

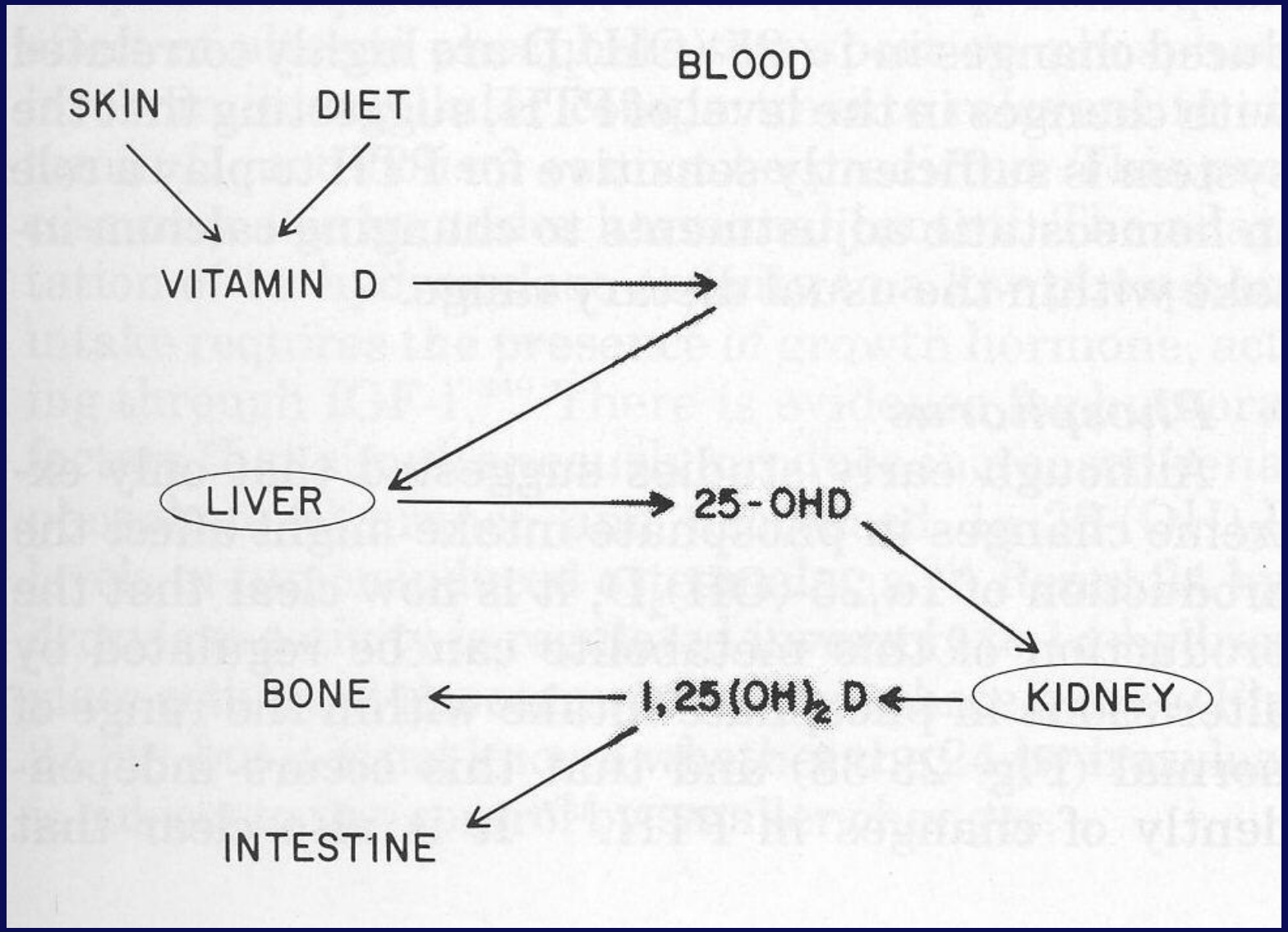


Ann Nutr Metab 2018;72:87–95

Anatomy and Feedback Inhibition



Transport and Metabolic Sequence of Activation of Vitamin D



Vitamin D Rich Foods

Box 1 | Sources of vitamin D

- Ultraviolet B sunlight exposure

  >90% of humankind's vitamin D supply is derived from ultraviolet B light
- Oily fish including trout, salmon, mackerel, herring, sardines, anchovies, pilchards, and fresh tuna

  Amount will depend on preparation, with smoked herring containing approximately 4 µg (160 IU) per 100 g and raw herring 40 µg (1600 IU) per 100 g
- Cod liver oil and other fish oils
- Egg yolk

  0.5 µg (20 IU) per yolk)
- Mushrooms

  Small quantities
- Supplemented breakfast cereals, mainly supermarket "own brands" in the UK

  Typically between 2 µg and 8 µg (80-320 IU) per 100 g
- Margarine and infant formula milk

  Statutory supplementation in the UK

BMJ 2010;340:b5664

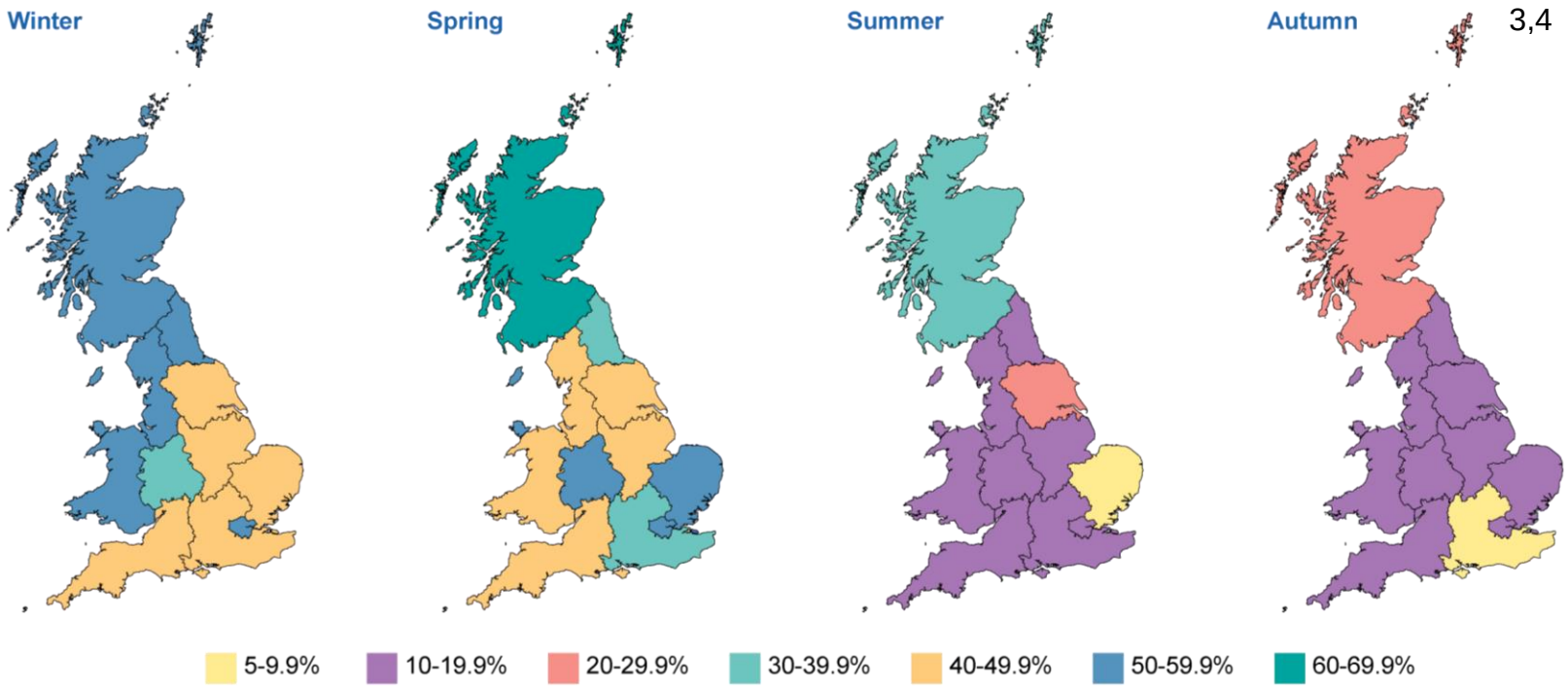
Prevalence

Vitamin D insufficiency is common in the UK population

There is a significant North-South gradient in the prevalence of vitamin D insufficiency/deficiency[1]

Even in summer and autumn, 28% of adult population in Scotland will be vitamin D insufficient, with 8% having severe deficiency[1]

Up to 50% of adult population in the UK will be vitamin D insufficient in winter and spring, with 16% having severe deficiency[2]



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1. Royal Osteoporosis Society Practical Guidelines. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. December 2018. Version 2
2. Fraser WD and Milan AM. Vitamin D assays: past and present debates, difficulties, and developments *Calcified Tissue Intl* 2013; 92(2): 118-127
3. Hyppönen E and Power C. *Am J Clin Nutr* 2007; 85(3): 860-8.
4. Pearce SHS and Cheetham TD. *BMJ* 2010 Jan 11; 340: b5664. doi:10.1136/bmj.b5664.

At Risk Groups

- Elderly, Institutionalised
- Malabsorption syndromes
- Bowel LTC/ Surgeries
- Obesity, Cancers
- Ethnicity ?
- Cultural aspects: Vegetarian, Religion, Prolonged Breast Feed
- Medications: Cholestyramine, Anti epileptic agents, Rifampicin, HAART, Steroids

Royal Osteoporosis Society Practical Guidelines. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. December 2018. Version 2

Measuring Vitamin D

- The best indicator of vitamin D exposure (from the diet and sunlight) is the serum concentration of 25(OH)D.

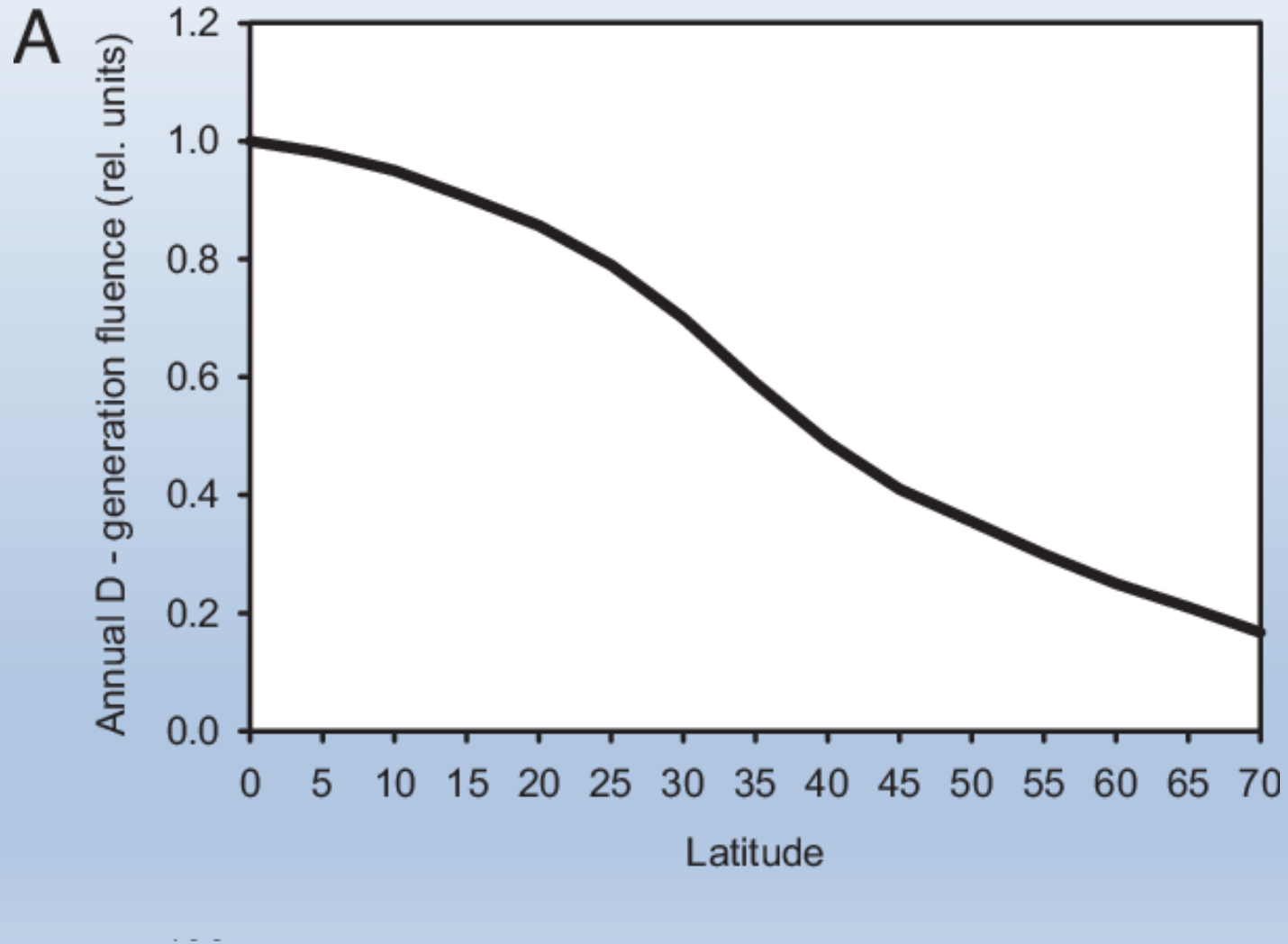
BMJ 2010;340:b5664
Vitamin D deficiency in adults - treatment and prevention, NICE 2016

Sunshine Vitamin

What Impacts Vitamin D Levels?

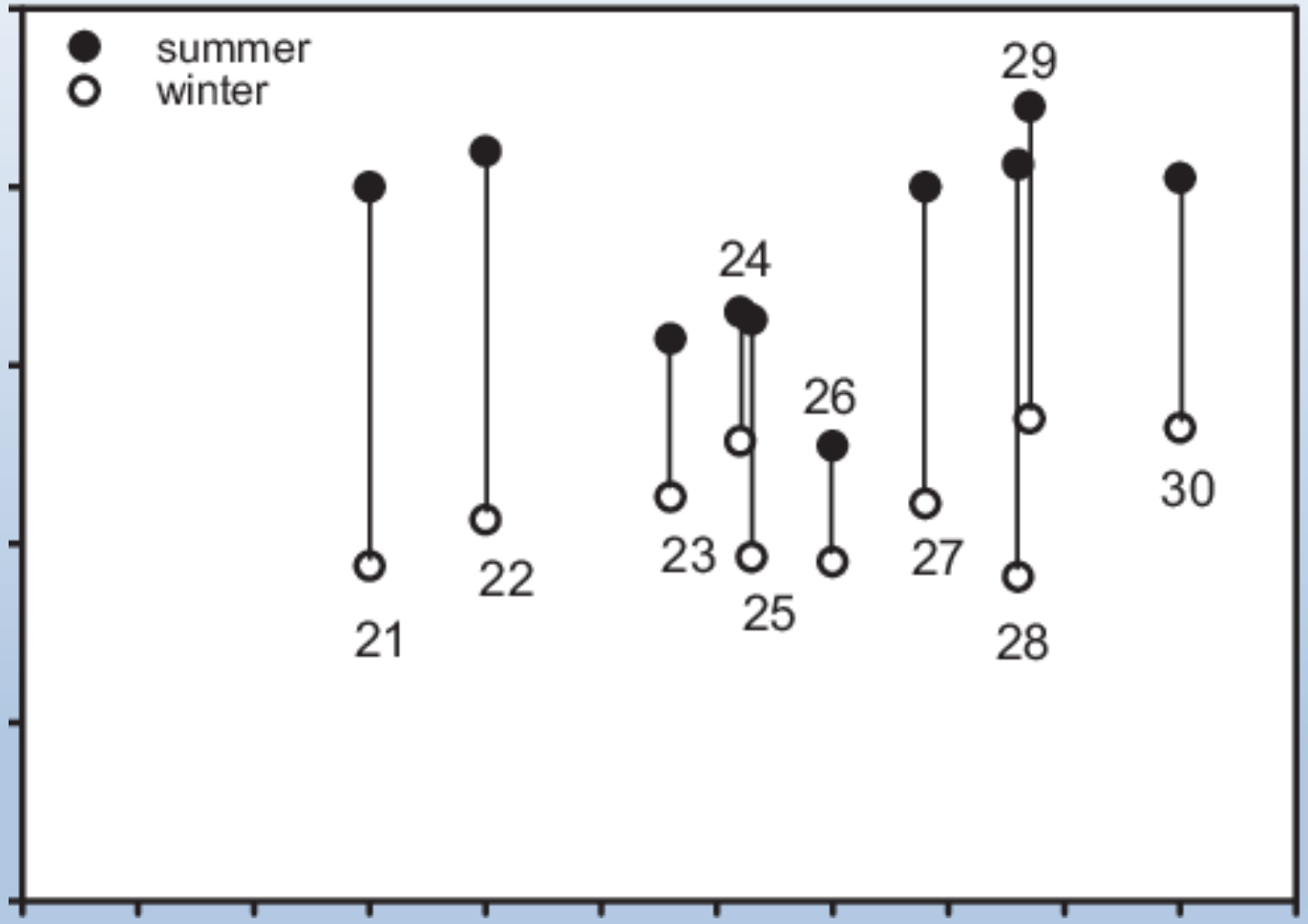
- Effect of daylight
- Exposure duration
- Clothing
- Skin pigmentation
- Effect of latitude

Latitude effect



Proceedings of the National Academy of Sciences 105(2):668-73

Seasonal changes



Proceedings of the National Academy of Sciences 105(2):668-73

Practical Sunlight Exposure

Summary for practical application of results (Scenario 2).

Exposures are assumed to occur during normal lunchtime hours (approximately 12–2 pm during British Summer Time, which is one hour either side of the solar noon).
Exposure should occur every day * during the months from March to September. If a day is missed, double exposure time should not be pursued the next day. If there is a wish to compensate, more skin area could be exposed but for the same short time.
Exposure should be in an open place if possible and in direct sun when available (i.e., without seeking shade for this short period).
Exposed skin should be unprotected (no sunscreen, make up, or clothing e.g., tights)
During the months June–August, about 1/3 of skin area should be exposed. This is equivalent to face, hands, forearms, and lower legs, but areas are interchangeable so if the face is protected then upper arms or upper chest might be exposed instead.
During the remaining cooler months, only hands and face (or equivalent) need to be exposed although larger areas would be an advantage when appropriate.
White-skinned people need a daily 9 min exposure.

* The calculations account for an all-weather climatology but little UV exposure will be gained during periods of heavy rain due to cloud cover. There is no need to get wet. Take exposure for the day when it is not raining or simply miss out on a very wet day.

Nutrients. 2018 Apr; 10(4): 497.

TR-012 (DoP July 2020)

Complications of Vitamin D Deficiency

MSK

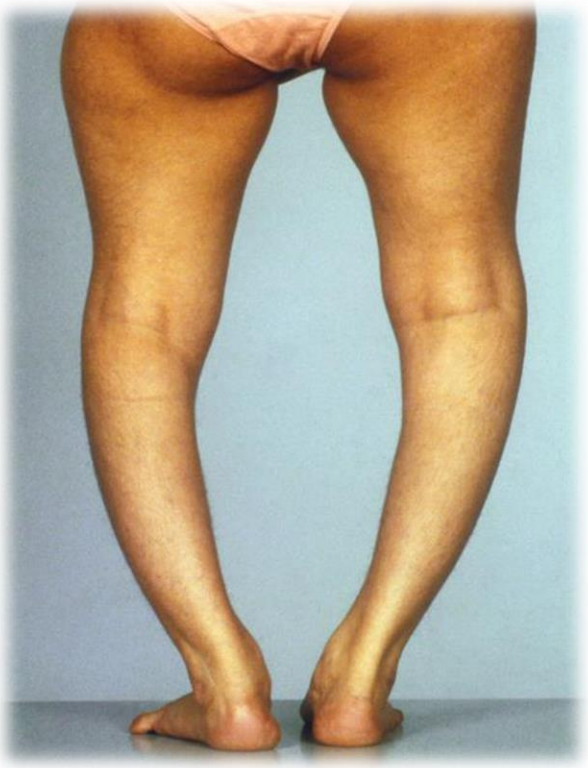
- Weakening of Bones
  - Osteomalacia
  - Osteoporosis exacerbation hypocalcaemia, secondary hyperparathyroidism, bone loss, muscle weakness, and falls and fragility fractures in older people

Royal Osteoporosis Society Practical Guidelines. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. December 2018. Version 2

Consequences of low vitamin D status in children

Prolonged and severe vitamin D deficiency results in significant risks to bone health due to a reduction in calcium absorption required for bone mineralisation.

In infants and children this defective mineralisation leading to bone softening at the growth plate of long bones (before they fuse) results in growth retardation and Rickets in growing children.



<u>Clinical manifestations of Rickets;</u>

- Widening of the bones at the wrists and knees
- Bowing of the legs
- Spine deformities
- Fractures, bone pain
- Dental abnormalities
- Severe cases can lead to seizures, convulsions, muscle spasms and cardiac events due to hypocalcemia – which can be fatal.

Dr. Paul Arundel and Prof. Nick Shaw (December 2018) Royal Osteoporosis Society: Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management in Children and Young People. Accessible online at https://theros.org.uk/clinical-publications-and-resources/

Prevalence of Vitamin D Deficiency and Insufficiency: A call to action from The former CMO Professor Dame Sally Davies

A study noted that though relatively uncommon, between September 2011 to September 2012 approximately one child has a seizure secondary to vitamin D deficiency per week in the UK.

The former Chief Medical Officer, Prof Dame Sally Davies, has asked the National Institute for Health and Care Excellence (NICE) to examine whether to introduce free vitamins for all under-fives. She said she believed it would be cost-effective, and was now necessary to reverse the “appalling” return of the disease (Rickets).

All UK Health Departments continue to recommend:

- **All** pregnant and breastfeeding women should take a daily supplement containing 10µg (400 IU) of vitamin D.
- **All** infants and young children aged 6 months to 5 years should take a daily supplement containing vitamin D in the form of vitamin drops. 400 IU daily is the recommended dose.

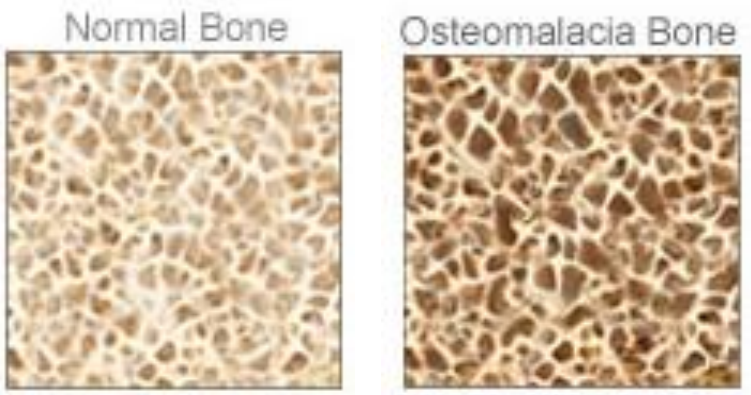
- Basatemur E, Sutcliffe A. *Archives of Disease in Childhood*. 2013 Jun;98(Suppl 1)
- https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/

Consequences of low vitamin D status in adults

Defective bone mineralisation leads to bone softening, occurring after growth plates have fused, leading to osteomalacia.

<u>Clinical manifestations of osteomalacia</u>

- bone pain (ostealgia)
- muscle weakness
- muscle pain (myalgia)
- joint pain (arthralgia)
- fatigue and malaise
- waddling gait due to pain in the hips
- head sweating
- secondary hyperparathyroidism

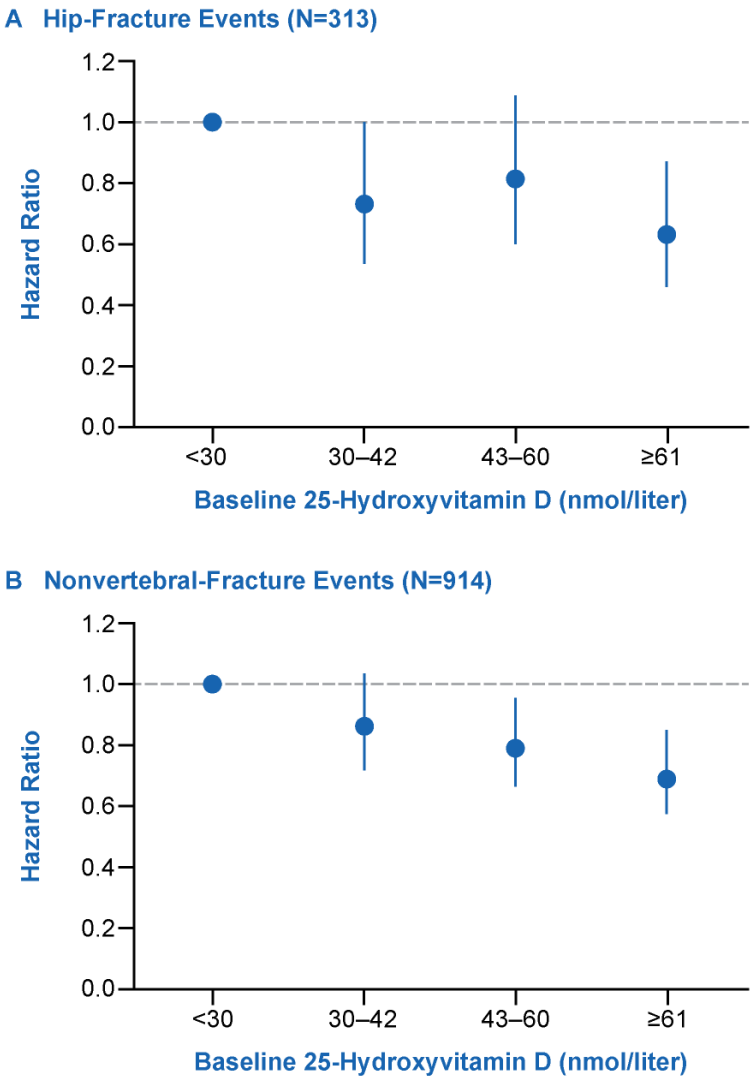


Rickets and osteomalacia are different manifestations of the same underlying pathological process. This may progress to a more severe deficiency if not medically managed and lead to a predisposition to osteoporosis.

The prevalence of osteomalacia histologically at postmortem in adult Europeans is as high as 25% however the true burden remains unidentified.

- Francis R, Aspray T, Fraser W, Macdonald H, Patel S, Mavroeidi A, *et al*. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. Royal Osteoporosis Society, December 2018.
- Vitamin D (serum, plasma) Association for Clinical Biochemistry 2012
- Uday, S and Hoegler, W 2017, 'Nutritional Rickets and Osteomalacia in the Twenty-first Century: Revised Concepts, Public Health, and Prevention Strategies' Current Osteoporosis Reports, vol. 15, no. 4, pp. 293–302.

Relationships between vitamin D and Fractures



Data shows that those > 65 years of age with baseline serum 25(OH)D levels of at least 61 nmol/L, as compared with persons with baseline levels of less than 30 nmol/L, had a risk of hip fracture that was reduced by 37% and a risk of any nonvertebral fracture that was reduced by 31%

With higher quartiles of baseline 25(OH)D levels, there was a significant trend toward lower risks of hip fracture ($p=0.02$) and any nonvertebral fracture ($p<0.001$).

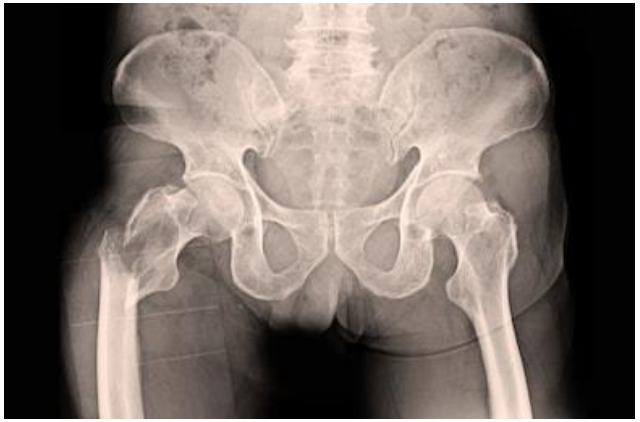
Bischoff-Ferrari HA et al. NEJM 2012; 367(1): 40-4

Persistently low vitamin D status predisposes >75 year old women to fractures

Swedish population based prospective study on BMD, falls, fractures

N = 987, final report available for 640 women (>75 years old)

Vitamin D Status (nmol/l)	10 year hip fracture incidence rates %
<50 (Low)	20.6
50-75 (Intermediate)	9.9
>75 (High)	6.9



- Buchebner, D et al (2014). Vitamin D insufficiency over 5 years is associated with increased fracture risk-an observational cohort study of elderly women. Osteoporosis International, 25(12), 2767-2775.

Non MSK Complications

Table 2 | Evidence for association of circulating 25-hydroxyvitamin D level or vitamin D supplementation with major health outcomes

	Design	Number of	Comparator	Odds/hazard ratio or relative risk§ (95% CI)
All cause mortality				
Autier and Gandini, 2007[10]	Meta-analysis of 18 vitamin D supplementation studies	57 311	Supplemented *v* unsupplemented	RR 0.93 (0.87 to 0.99)
Ginde et al, 2009[12]	Prospective observational study in individuals >65 years*	3265	Serum 25-OHD concentration >100 nmol/l *v* <25 nmol/l	HR 0.55 (0.34 to 0.88)
Dobnig et al, 2008[13]	Prospective cohort study with coronary angiography†	3258	Median serum 25-OHD concentration 70 nmol/l *v* 19 nmol/l‡	HR 0.48 (0.37 to 0.630
Cardiovascular mortality				
Ginde et al, 2009[12]	Prospective observational study in individuals >65 years*	3265	Serum 25-OHD concentration >100 nmol/l *v* <25 nmol/l	HR 0.42 (0.21 to 0.85)
Dobnig et al, 2008[13]	Prospective cohort study with coronary angiography†	3258	Median serum 25-OHD concentration 70 nmol/l *v* 19 nmol/l‡	HR 0.45 (0.32 to 0.64)
Diabetes				
Type 1 Zipitis and Akobeng, 2008[18]	Meta-analysis of four case-control studies of vitamin D supplementation	6455	Supplemented *v* unsupplemented	OR 0.71 (0.60 to 0.84)
Type 2 Pittas et al, 2007[14]	Meta-analysis of four observational studies	6784 (non-black)	Serum 25-OHD concentration 63-95 nmol/l *v* 25-58 nmol/l	OR 0.36 (0.16 to 0.80)
Cancer				
Colorectal Yin et al, 2009[15]	Meta-analysis of six case-control studies	3556	Per 50 nmol/l increase in serum 25-OHD concentration	OR 0.57 (0.43 to 0.76)
Breast				

Vit D as independent predictors for progression to T2DM at 12 months

Biomarker	Odds Ratio (95% CI)	P value
TNFα	1.09 (1.00- 1.18)	0.044
IL 6	1.01 (0.87- 1.17)	0.991
Adiponectin	0.94 (0.90- 0.99)	0.032
Leptin	1.01 (0.99- 1.03)	0.197
Vitamin D	0.99 (0.98- 1.0)	0.093
CRP	1.03 (0.99- 1.07)	0.097

Srinivasan et al 2011.

Ethnic influences in Vitamin D

Variables	R	Unstandardised coefficient (B)	95% (CI)	p value
TNF	0.22	1.08	1.06 to 1.30	0.012
IL6	0.354	1.36	1.19 to 1.55	<0.001
Adiponectin	0.554	-1.09	-1.20 to 1.02	0.106
Leptin	0.730	1.32	1.16 to 1.51	<0.001
CRP	0.327	1.16	-1.15 to 1.51	0.300
Vitamin D	0.654	-1.14	-1.25 to -1.03	<0.001

Srinivasan et al 2011.

COVID-19

There is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19.

However, all people should continue to follow UK Government advice on daily vitamin D supplementation to maintain bone and muscle health during the COVID-19 pandemic.

www.nice.org.uk/guidance/es28 June 2020

There was Insufficient Evidence from Non-musculoskeletal Health Outcomes

Vitamin D deficiency in adults - treatment and prevention, NICE.

Who to Test

- Do not routinely test for vitamin D deficiency
- Test for vitamin D deficiency, by measuring serum 25-hydroxyvitamin D (25[OH)D) levels, if a person presents with symptom
- Test for vitamin D deficiency if there is a clinical reason to do so

(NICE vs SACN)

- PHPT

Royal Osteoporosis Society Practical Guidelines. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. December 2018. Version 2

Level of deficiency	25 hydroxyvitamin D level	Recommended treatment
Severe deficiency (associated with osteomalacia including rickets in children and osteoporosis and fractures in adults)	<25 nmol/l 25 hydroxyvitamin D	Capsule formulations: Dose: 40,000 IU weekly for 7 weeks. Preferred products: *Aviticol* 20,000IU capsules *Fultium D3* 20,000IU capsules *Plenachol* 20,000IU and 40,000IU capsules Liquid formulations Dose: 50,000IU weekly for 6 to 8 weeks. Preferred products: *InVita D3* oral solution 25,000IU in 1ml *Thorens* oral solution 25,000IU in 2.5ml
Deficiency associated with disease risk	25-50 nmol/l 25 hydroxyvitamin D	If symptoms are severe, treat with preferred products and licensed doses detailed above. If physical symptoms are milder, lower doses are indicated Dose: 800-1600 IU daily for 12 weeks. Preferred products: *Desunin* 800IU tablets *Fultium D3* 800IU capsules
Insufficiency	50-75nmol/l 25 hydroxyvitamin D	If physical symptoms are present, prescribe 800-1600 IU daily for 12 weeks (as detailed above). If patient has no physical symptoms, consider lifestyle advice including: increased dietary intake and safe sun exposure (see *PACE Bulletin* Vol 6 No 6 Prevention of vitamin D deficiency in at-risk groups (May 2012)).
Replete	>75nmol/l 25 hydroxyvitamin D	No treatment necessary

Note: The immunoassay used in the Path Links laboratories does not detect D2 (ergocalciferol) or D3 (colecalciferol), instead it measures the 25 hydroxylated metabolite.

PACEF 2015. Available at: https://lincolnshire-pacef.nhs.uk/key/pacef/760-pace-bulletin-vol-9-no-13-vitamin-d-treatment/file

What Constitutes Vitamin D Deficiency & Insufficiency?

Royal Osteoporosis Society definitions and treatment recommendations		
Plasma 25(OH)D <25nmol/L*	Deficient	**Treatment recommended**
Plasma 25(OH)D 25–50nmol/L*	May be inadequate in some people	**Treatment is recommended in patients with the following:** • fragility fracture, documented osteoporosis or high fracture risk • treatment with antiresorptive medication for bone disease • symptoms suggestive of vitamin D deficiency • increased risk of developing vitamin D deficiency in the future because of reduced exposure to sunlight, religious/cultural dress code, dark skin, etc. • raised PTH • medication with antiepileptic drugs or oral glucocorticoids
Plasma 25(OH)D >50nmol/L	Sufficient for almost the whole population	**Provide reassurance and give advice on maintaining adequate vitamin D levels through safe sunlight exposure and diet**

*Reference levels may differ in this range.

- Royal Osteoporosis Society Practical Guidelines. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. December 2018. Version 2

Maintenance Therapy

Maintenance treatment

Maintenance therapy is indicated for:

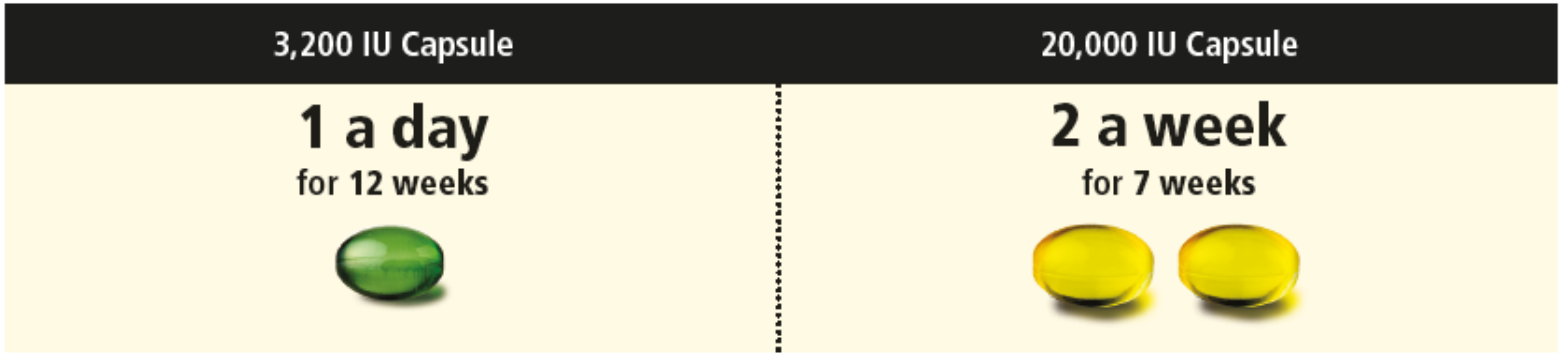
- **Those diagnosed with and treated for severe deficiency (i.e. those with pre-treatment levels of 25 hydroxyvitamin D of <25nmol/l and those with pre-treatment levels of 25 hydroxyvitamin D of between 25-50nmol presenting with severe symptoms and treated with the higher doses of colecalciferol).**
- **Those with pre-treatment levels of 25-50 nmol/l 25 hydroxyvitamin D or 50-75nmol/l 25 hydroxyvitamin D once deficiency has been corrected, if they are still considered at risk (e.g. housebound patients).**

Patients who have been successfully treated for vitamin D deficiency for whom prescribed maintenance therapy is not indicated, should be encouraged to make lifestyle changes such as increasing dietary intake of vitamin D, increasing safe sun exposure and increasing vitamin D intake with supplements purchased from community pharmacies, health food stores or other reputable retailers (see *PACE Bulletin* Vol 6 No 6 Prevention of vitamin D deficiency in at-risk groups (May 2012)).

Recommended treatment strategy for treating and preventing vitamin D deficiency in adults

The ROS recommend fixed-loading doses and maintenance therapy when treating deficiency in adults.

Loading Doses (Adults)
Up to a total of approximately 300,000 IU given either as weekly or daily split doses



For many patients who are at risk of vitamin D deficiency but are not showing obvious symptoms, loading doses may not be needed, and lower maintenance doses should be prescribed. e.g. 800 IU/day

Maintenance Doses
Once replete, a maintenance dose is recommended, and should normally be started within 1 month after last loading dose.

- Royal Osteoporosis Society Practical Guidelines. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. December 2018. Version 2

Why prescribe a licensed vitamin D for at-risk patients and not a food supplement?

Advice from the Royal College of Physicians and the General Medical Council is that wherever possible, a licensed medicine should be supplied[1,2]

Studies have shown food supplements may have variable content[3]

- Tablets from different batches ranged from 9% to 140% of the stated dose
- Tablets from the same bottle contained 52% to 135% of stated dose
- Only 1/3 of the tablets analysed were within 10% of the stated dose

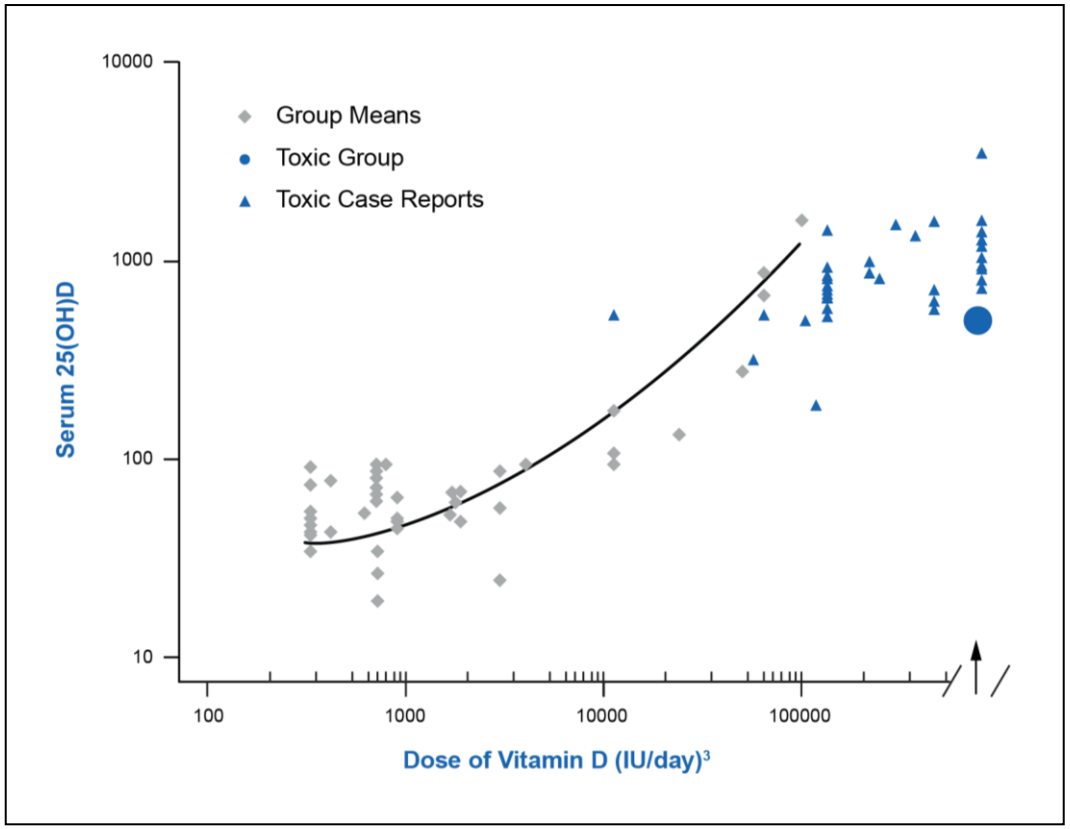
Licensed medicines have dedicated medical information services which provide information within 24hrs[4]

Licensed medicines adhere to MHRA Yellow Card reporting[4]

1. http://www.rpharms.com/archive-documents/factsheet5.pdf.
2. https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicinesanddevices/prescribing-unlicensed-medicines
3. Taylor, PN and Davies JS. (2018) A review of the growing risk of vitamin D toxicity from inappropriate practice. British Journal Clinical Pharmacology: 84(6):1121-1127
4. https://yellowcard.mhra.gov.uk/the-yellow-card-scheme

Safety of vitamin D treatment in the licensed form

- **Vitamin D is well known and has been widely used in clinical practice for many years[1]**



Toxicity is most likely to occur in chronic overdosage where hypercalcaemia could result[2]

- Doses above 10,000 IU/day are associated with toxicity
- Doses ≥50,000 IU/day for several weeks or months are frequently associated with toxicity, including documented hypercalcaemia

1. Data on file. Internis Pharmaceuticals Ltd.
2. Vieth, R. (2009) Vitamin D and Cancer Mini-Symposium: The Risk of Additional Vitamin D. Annals of Epidemiology. Vol. 19, Issue 7: 441-445

Monitoring Treatment

Monitoring requirements

- If pre-treatment levels of 25 hydroxyvitamin D were <25 nmol/l then check 25-hydroxyvitamin D, parathyroid hormone (PTH) and calcium levels, 4 to 6 months after initiation of treatment. At this stage, patients should have been receiving initial high dose treatment for a period of 6 to 8 weeks depending on which product was prescribed and maintenance doses thereafter. If the patient is within reference range there is no need to repeat test. If any of the values are outside of reference range, refer to an endocrinologist.
- Low calcium levels could indicate primary hyperparathyroid disease.
- High calcium levels could be indicative of another underlying condition.
- PTH levels outside of normal range could be indicative of parathyroid disease.
- If pre -treatment levels of 25 hydroxyvitamin D were <50 nmol/l there is no requirement to re-test levels unless symptoms persist following treatment.
- If patients PTH levels were >10 at baseline, re-check at 4 to 6 months regardless of treatment group to exclude the possibility of parathyroid disease. If PTH levels remain elevated whilst vitamin D levels are normal, refer to an endocrinologist.

Differential Diagnosis

- Painful weakness
  - Bone Ca
  - Secondary in bone
  - Myeloma
  - Fragility Fractures
  - Fibromyalgia
  - PMR
  - PHPT
  - RA
  - Osteomyelitis
  - Paget's Disease
- Painless Weakness
  - Dermatomyositis
  - Polymyositis
  - Muscular Dystrophy
  - Thyroid Disease
  - Rare endocrine conditions: Cushing's' syndrome

Referral

Specialist referral

Specialist referral will be necessary in patients with:

- Liver disease.
- Renal disease, including the presence of renal stones.
- Hypercalcaemia
- Metastatic cancer.
- Lymphoma.
- Sarcoidosis.
- Tuberculosis.
- Skeletal deformity.
- Short stature.
- Focal bone pain.
- Suspicion of malabsorption

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Colecalciferol 3,200 IU equivalent to 80µg
Colecalciferol 20,000 IU equivalent to 500µg
Colecalciferol 2,740 IU/ml (equivalent to 68.5µg/ml)
Colecalciferol 800 IU equivalent to 20µg

Please refer to Fultium-D_3 SmPC for full licenced indications as some topics in this presentation are not indicated.

3,200 IU Vitamin D in Pregnancy and Adolescents >12 Years

Those needing loading dose (in Pregnancy) - should take 1 capsule (3,200 IU) daily for up to 12 weeks dependent upon the severity of the disease and the patient's response to treatment.

Those needing loading dose (in adolescence age >12) - should take 1 capsule (3,200 IU) daily for up to 12 weeks dependent upon the severity of the disease and the patient's response to treatment. **LICENCED**

Use care when prescribing in pregnancy, as high doses of colecalciferol may affect the fetus.

- Fultium-D_3 3,200 IU capsules. Summary of Product Characteristics. January 2018

Fultium-D_3 800 IU Capsules[1]

- Prescription medicine indicated for the prevention and treatment of vitamin D deficiency[1]
- Simple one a day treatment dose.
- Suitable for adolescents, adults and elderly.
- Easy-to-swallow and identifiable capsules to help aid compliance.
- Suitable for use in pregnancy and breastfeeding.
- Suitable for storing up to 10 days in a dossette box.[2]
- The capsule gelatin is halal and kosher certified.[3]

Available on NHS contract

To ensure your patients always receive a licensed product
ALWAYS RX FULTIUM-D_3 BY BRAND NAME

Fultium®-D_3

Use care when prescribing in pregnancy, as high doses of colecalciferol may affect the fetus.

1. Fultium-D3 800 IU capsules. Summary of Product Characteristics. January 2018
2. Data on file. D1. Internis Pharmaceuticals Limited.
3. Data on file. R1. Internis Pharmaceuticals Limited.

Summary

- Vitamin D insufficiency is common in the UK
- Deficiency typically presents rickets or hypocalcaemia in infancy and childhood, and MSK pain, weakness, tiredness pain in adults
- CVD, HT, T2DM, AI conditions and cancers associated with vitamin D insufficiency
- Treat rickets and osteomalacia with high strength calciferol for 8-12 weeks, followed by regular vitamin D supplements

Fultium-D_3 Abbreviated Prescribing Information

Fultium-D_3 800 IU, 3,200 IU & 20,000 IU Capsules Abbreviated Prescribing Information

Please refer to the appropriate Summary of Product Characteristics (SmPC) before prescribing Fultium-D_3. Use care when prescribing in pregnancy, as high doses of colecalciferol may affect the fetus.

Fultium-D_3 Capsules: Each Fultium-D_3 800 IU capsule contains colecalciferol 800 IU equivalent to 20 micrograms vitamin D_3. Each Fultium-D_3 3,200 IU capsule contains colecalciferol 3,200 IU equivalent to 80 micrograms vitamin D_3. Each Fultium-D_3 20,000 IU capsule contains colecalciferol 20,000 IU equivalent to 500 micrograms vitamin D_3. **Indication:** Fultium-D_3 800 & 20,000 IU capsules. Prevention and treatment of vitamin D deficiency. As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency. Fultium-D_3 3,200 IU capsules only. Treatment of vitamin D deficiency. **Dosage and administration:** Adults and the elderly. Treatment of Vitamin D deficiency (serum levels <25nmol/l (<10ng/ml)). Depending on the severity of the disease and the patient's response to treatment: 1-4 Fultium-D_3 800 IU capsules daily for up to 12 weeks or 1 Fultium-D_3 3,200 IU capsule daily for up to 12 weeks or 2 Fultium-D_3 20,000 IU capsules per week for 7 weeks. Prevention of vitamin D deficiency. 1-2 Fultium-D_3 800 IU capsules (800-1600IU) daily or 1 Fultium-D_3 20,000 IU capsule per month. Long term maintenance therapy following deficiency treatment or vitamin D insufficiency (serum levels 25-50nmol/l (10-20 ng/ml). 1-2 Fultium-D_3 800 IU capsules daily. Children over 12 years. Depending on the severity of the disease and the patient's response to treatment: 1 Fultium-D_3 800 IU capsule daily (for prevention/ treatment), or 1 Fultium-D_3 3,200 IU capsule daily for up to 12 weeks (treatment), or 1 Fultium-D_3 20,000 IU every 6 weeks (prevention), or 1 Fultium-D_3 20,000 IU every 2 weeks to 6 weeks (treatment). Should only be given under medical supervision. **Not recommended for use in children under 12 years.** For oral use. Swallow capsules whole with water. **Contraindications:** Hypersensitivity to vitamin D or any of the excipients in the product; hypervitaminosis D; nephrolithiasis; diseases or conditions resulting in hypercalcaemia and/or hypercalciuria; severe renal impairment. **Warnings and Precautions:** Use with caution in patients with impaired renal function or sarcoidosis and monitor the effect on calcium and phosphate levels. In patients with severe renal insufficiency, vitamin D in the form of colecalciferol is not metabolised normally and other forms of vitamin D should be used. In cases of long-term daily doses exceeding 1,000 IU, monitor serum calcium levels. Use caution in patients receiving treatment for cardiovascular disease. Consider vitamin D supplementation from other sources. **Interactions:** Concomitant treatment with phenytoin, barbiturates and glucocorticoids can decrease the effect of vitamin D. Attenuation of digitalis and other cardiac glycosides. Absorption of vitamin D may be reduced by ion exchange resins and laxatives. **Pregnancy and lactation:** Use only under medical supervision. Studies have shown safe use up to 4,000 IU daily but reproductive toxicity has been seen in animal studies. The 20,000 IU dose should not be used during pregnancy. Vitamin D is excreted in breast milk, when prescribing additional vitamin D to a breast-fed child consider the dose of any additional vitamin D given to the mother. **Undesirable effects:** Allergic reactions are possible. Uncommon adverse reactions include hypercalcaemia and hypercalciuria. Rare adverse reactions include: pruritus rash and urticaria. **Overdose:** Refer to SmPC. **Legal Category:** POM. **Pack size:** Fultium-D_3 800 IU capsules x 30 – NHS Price £3.60. Fultium-D_3 800 IU capsules x90 – NHS Price £8.85. Fultium-D_3 3,200 IU capsules x30 – NHS Price £13.32. Fultium- D_3 3,200IU capsules x90 – NHS Price £39.96. Fultium-D_3 20,000 capsules x15 – NHS Price £17.04. Fultium-D_3 20,000 capsules x30 – NHS Price £29.00. **MA Number:** 40861/0002 [Fultium-D_3 800 IU capsules]. 40861/0003 [Fultium-D_3 3,200 IU capsules]. 40861/0004 [Fultium-D_3 20,000 IU capsules]. **MA Holder:** Internis Pharmaceuticals Ltd. Linthwaite Laboratories, Linthwaite, Huddersfield, West Yorkshire HD7 5QH, UK. *Full Prescribing Information is available from Internis Pharmaceuticals Ltd.* **Date of preparation:** August 2018. unique ID no. FUL-458.

Fultium-D_3 Drops
Abbreviated Prescribing Information

Please refer to the appropriate Summary of Product Characteristics (SmPC) before prescribing Fultium-D_3. Use care when prescribing in pregnancy, as high doses of colecalciferol may affect the fetus.

Fultium-D_3 Drops: 1 ml of oral solution contains 2740 IU (68.5 mcg per ml) colecalciferol; 3 drops contains 200 IU colecalciferol. **Indications:** Prevention and treatment of vitamin D deficiency in adults and children, and as an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency. **Dosage and administration:** For oral use. Can be taken directly or mixed with a small amount of food. *Adults.* Treatment of deficiency: 12 - 60 drops (800-4000 IU) daily; During pregnancy and breast-feeding: 6-60 drops (400-4000 IU) daily; Osteoporosis adjunctive therapy: 12 drops (800 IU) daily. Maintenance or prevention of deficiency: 12 - 24 drops (800-1600 IU) daily; During pregnancy and breast-feeding: 6-30 drops (400-2000 IU) daily. Children. Treatment of deficiency: 0-2 years: 6-15 drops (400-1000 IU) daily; 2-11 years: 6-30 drops (400-2000 IU) daily; 12-18 years: 6-60 drops (400-4000 IU) daily. Maintenance or prevention of deficiency: 0-2 years: 3-15 drops (200-1000 IU) daily; 2-11 years: 6-15 drops (400-1000 IU) daily; 12-18 years: 6-24 drops (400-1600 IU) daily. **Contraindications:** Hypersensitivity to vitamin D or any of the excipients; hypervitaminosis D; nephrolithiasis; diseases or conditions resulting in hypercalcaemia and/or hypercalciuria; severe renal impairment. **Warnings and Precautions:** Use caution in patients with impaired renal function or sarcoidosis. Monitor effect on calcium and phosphate levels in these patients. Consider risk of soft tissue calcification. Use other forms of vitamin D in cases of severe renal insufficiency. Consider the need for calcium supplementation in individual patients. Where calcium supplementation is necessary, close medical supervision is required. Use caution in patients receiving treatment for cardiovascular disease. Make allowances for vitamin D supplementation from other sources. Monitor to prevent hypercalcaemia. **Interactions:** Concomitant phenytoin, barbiturates and glucocorticoids can decrease the effect of vitamin D. Ion exchange resins, laxatives, actinomycin and imidazole may also reduce the effect of vitamin D. Oral calcium and vitamin D potentiates the effect of digitalis and other cardiac glycosides. **Pregnancy and lactation:** Limited clinical data in pregnancy. Animal studies have shown reproductive toxicity. RDI in pregnancy is 400 IU. Pregnant women who are vitamin D deficient may need a higher dose. Pregnant women should follow the advice of their GP, as their requirements may vary depending on disease severity and response to treatment. Vitamin D and metabolites are excreted in breast milk. Overdose in nursing infants has not been observed, however, when prescribing additional vitamin D to a breast-fed child, consider the maternal dose of any additional vitamin D. **Undesirable effects:** Hypercalcaemia and hypercalciuria. Refer to the SmPC for the full list of side effects. **Legal Category:** POM. **Pack size:** Fultium-D_3 Drops, 1 x 25 ml – NHS Price £10.70. **MA Number:** 40861/0005. **MA Holder:** Internis Pharmaceuticals Ltd. Linthwaite Laboratories, Linthwaite, Huddersfield, West Yorkshire HD7 5QH, UK. *Full Prescribing Information available.* **Date of preparation:** August 2018. *unique ID no.* FUL-263.

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or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to 01484 848164.