Vitamin D3

Science and Supplements

Prof Em Peter Cobbold
Ruthin U3A
30 January 2018

(archived on web site)
Common knowledge

- the sunshine vitamin
- codliver oil on a teaspoon
- rickets
- osteoporosis

Online fora are an unreliable source of information.
“I take multivitamins so I’m OK for D3”

..perhaps,

but do you *know* you take enough D3?

25% of over-65s are D3-deficient, even by low UK criteria. 75% by German criteria.

The RDA is for adults not the elderly, who absorb fewer nutrients.
VitD is HOT science!

5000 per year now
Tissues that respond to D3

- plus BRAIN, nerves, skeletal muscle, immune system.....

- 37 tissues express VitD receptors.

- 300+ genes are controlled by D3
D3 molecules

What are these?
Vitamin D3 was discovered between 1922 and 1936.

D3 from diet or from sun on skin and stored in fat

**Activation** by adding hydroxyl group (OH) to #25 Carbon in liver and #1 in kidney etc
D3 signalling is complex....

1,25(OH)D3 binds to VDReceptor which then binds to DNA....
1,25(OH)D₃ is a hormone – with many actions.

for example, protecting brain cells in PD and AlzD.

M J Berridge (2016) http://europepmc.org/articles/PMC4938033
Diseases and conditions in which D3 is involved
D3 and disease

- Huge compendium of information with selected science reports, for a non-scientific audience, here:
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<td><strong>Rheum. Arth (76+) Overview</strong></td>
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Diseases and conditions in which D3 is involved

A NUMBER TO REMEMBER:

50 nmol/Litre

- the serum 25(OH)D3 level regarded as adequate by PHE since 2016

- compare with research data that follow
D3 for fighting infections

eg Sepsis

“....patients with vitamin D deficiency (25(OH)D < 15-20 ng/mL *) ... have higher odds of sepsis compared to individuals without vitaminD deficiency”

“......deficiency in 25(OH)D and 1,25(OH)2D were significant predictors of 30-day mortality in septic patients”

source: europepmc.org/articles/PMC4455341/

* 20 ng/ml = 50 nmol/L
D3 helps fight viruses

Serum 25-Hydroxyvitamin D and the Incidence of Acute Viral Respiratory Tract Infections in Healthy Adults

James R. Sabetta, Paolo DePetrillo, Ralph J. Cipriani, Joanne Smardin, Lillian A. Burns, and Marie L. Landry

Yale Univ School of Medicine
People with higher serum D3 get 5-fold fewer Upper Respiratory Tract infections.

Two groups, above (red) or below (green) 38 ng/ml = 100 nmol/L:

- High: 10% infected
- Low: 50% infected

Days into winter: mid-Sept to mid-Jan
Canadian GP treats seasonal 'flu with D3

- Letter in Canadian Family Physician June 2015 vol. 61 no. 6 507

- Gerry Schwalfenberg, MD CCFP FCFP, Edmonton, Alberta, Canada

“A colleague of mine and I have introduced vitamin D at doses that have achieved greater than 100 nmol/L in most of our patients for the past number of years, and we now see very few patients in our clinics with the flu or influenzalike illness. In those patients who do have influenza, we have treated them with the vitamin D hammer, as coined by my colleague. This is a 1-time 50 000 IU dose of vitamin D3 or 10 000 IU 3 times daily for 2 to 3 days. The results are dramatic, with complete resolution of symptoms in 48 to 72 hours. One-time doses of vitamin D at this level have been used safely and have never been shown to be toxic.”
Frailty in the elderly

• frailty may be a sign of D3 deficiency
• and the elderly are more susceptible to many conditions.................
Vitamin D is a secosteroid hormone. Vitamin D receptors are present in the majority of body tissues. The manifestations of hypovitaminosis D - linked to dysfunction of target tissues - are various, including osteoporosis, cancer, tuberculosis, hypertension, multiple sclerosis, depression, dementia, sarcopenia, propensity to fall... The serum 25-hydroxyvitamin D threshold value to avoid these adverse health events is around 30 ng/mL. Only 15% of the elderly reach this target concentration. For the remaining 85% with no supplements, the severity of hypovitaminosis D appears to be a biomarker of chronic diseases and of frailty. Conversely, the supplementation for correction of hypovitaminosis D positively impacts bone and non-bone morbidities - such as risks of falls and fractures - and reduces the mortality rate. A daily intake of at least 800-1,000 U supplemental vitamin D(3) per day is the key.
Low D3 increases risk of Alzheimer's or dementia

- 2014 study** showed that a low vitamin D level was associated with a high risk of dementia and Alzheimer’s disease.
  - Vitamin D level of less than 25 nmol/L: 122% increased risk of Alzheimer’s
  - Vitamin D level 25 to 50 nmol/L: 51% increased risk of Alzheimer’s

http://www.askdrray.com/vitamin-d3-protects-your-brain/
** https://www.ncbi.nlm.nih.gov/pubmed/25098535
VitD and Alzheimer's – reversal of amyloidβ accumulation. (Dec 2017)

- Epidemiological studies suggest a tight link between hypovitaminosis of vitamin D and AD
- D3 decreased Amyloidβ-production and increased Aβ-degradation in neuroblastoma cells or vitamin D deficient mouse brains.
- Our results further strengthen the link between AD and vitamin D, suggesting that supplementation of vitamin D or vitamin D analogues might have beneficial effects in AD prevention.

- europepmc.org/abstract/MED/29257109
Dementia and VitD
pages on VitaminDwiki

- Cognitive category listing has 185 items along with related searches
- Poor cognition associated with low vitamin D in elderly (Asians now too) – meta-analysis March 2016
- Memory loss linked to low vitamin D – Nov 2015
- Dementia risk significantly increased if have 4 chronic diseases – all associated with low vitamin D – Sept 2015
- Dementia associated with low vitamin D in two thirds of studies – systematic review May 2013
- Cognitive Impairment 4X more likely if low vitamin D (less than 20 ng) – Feb 2014
- Brain (Alzheimer’s) worked better with Vitamin D intervention – meta-analysis July 2013
- Dementia surprisingly associated with low vitamin D (should not a surprise) – Aug 2014
- Low vitamin D associated with cognition in women who were 5 years older – Oct 2013
- 'Senior moment" 25X more likely with low vitamin D – Feb 2012
- Fewer white spots in MRI brain scans if had more vitamin D – Jan 2014
- Search VitaminDWiki for demntia anywhere in text 484 items Jan 2016
- Search VitaminDWiki for dementia in title 19 items as of Jan 2016
- Dementia less likely with increased levels of Magnesium etc.
- 3rd most common dementia perhaps might also be associated with low vitamin D: Lewy Body
- Cognitive impairment 4X more likely when vitamin D less than 10 ng – Nov 2010
Vitamin D3 and depression
MJ Berridge. Pharmacol Reviews 2017
http://pharmrev.aspetjournals.org/content/69/2/80

1,25(OH)2D3 (Vitamin D)

Vitamin D-sensitive processes that prevent depression

- Controls expression of calcium homeostasis genes:
  - Increases expression of Calbindin, parvalbumin, NCX1, PMCA
  - Decreases expression of CaV1.2

- Controls expression of antioxidant genes:
  - Nrf2, G6PD, Gpx, TR, GSH, gamma-GT, GCLC, GR

- Controls formation of serotonin:
  - Increases expression of TPH2 and represses TPH1

- Controls inflammation:
  - Reduces expression of inflammatory cytokines

- Controls expression of mitochondrial proteins:
  - Maintains mitochondrial respiration

cf SSRIs eg Prozac
CONCLUSION:

Vitamin D deficiency** is associated with the presence of at least 1 Lower Urinary Tract Symptoms. LUTSymptoms included nocturia, incomplete emptying, hesitancy, and urinary incontinence.

**deficiency <50nmol/L
Skeletal muscle weakness

Table 8. Conclusions and outstanding questions

Conclusions

Vitamin D exerts rapid and genomic effects in primary muscle cells and cell lines. These effects relate to intracellular calcium handling, differentiation and contractile protein composition. In vivo, it is not clear whether VDR is expressed in adult skeletal muscle.

Whole-body VDRKO mice and vitamin D-deficient animals display significant defects in muscle function and development. In humans, single nucleotide polymorphisms in the gene encoding VDR have been associated with differences in muscle strength. Changes in muscle morphology in humans with severe vitamin D deficiency have been reported since the 1970’s.

Proximal myopathy and muscle pain in subjects with severe vitamin D deficiency resolve following vitamin D supplementation.

2000 IU pd resolved PC's in 6 weeks
Abstract  Ageing can occur at different rates, but what controls this variable rate is unknown. Here I have developed a hypothesis that vitamin D may act to control the rate of ageing. The basis of this hypothesis emerged from studying the various cellular processes that control ageing. These processes such as autophagy, mitochondrial dysfunction, inflammation, oxidative stress, epigenetic changes, DNA disorders and alterations in Ca\(^{2+}\) and reactive oxygen species (ROS) signalling are all known to be regulated by vitamin D. The activity of these processes will be enhanced in individuals that are deficient in vitamin D. Not only will this increase the rate of ageing, but it will also increase the probability of developing age-related diseases such as Alzheimer’s disease, Parkinson’s disease, multiple sclerosis and cardiovascular disease. In individuals with normal vitamin D levels, these ageing-related processes will occur at lower rates resulting in a reduced rate of ageing and enhanced protection against these age-related diseases.
Serum D3: ADEQUACY or DEFICIENCY?
D3 adequate or deficient?

- What is a good serum level of 25(OH)D3?

- **Measure** your serum 25(OH)D3. Cityassays, part of PHLS, Birmingham supply postal kit for £28. www.vitamindtest.org.uk

- Late winter (J-F-M) is best time of year to measure as serum level will be at its lowest.

- The concentration is given as nmol/L: “nanomole per litre”
 Measure your blood D3

£28 test done through the post by a PHLS lab in Birmingham

Measure blood 25(OH)D3

Now, late winter, is best time to measure.

www.cityassays.org.uk

For further details visit our website www.vitamindtest.org.uk

Pathology Department City Hospital, Dudley Road, Birmingham
Serum 25(OH)D3: UK guidelines, nmol/L

- **Severe deficiency:** < 15
- **Deficiency:** 15 to 30
- **Insufficiency:** 30 to 50
- **Adequate:** >50
  - **High:** >220 (increased risk of toxicity)

UK guidelines are consistently lower than USA, Canada, Germany. 50 is found to be a risk level in much research (eg slides 18,20,23,24, ).

- Older values are often given in ng/ml. Multiply ng/ml by 2.5 to get nmol/L. So 40ng/ml is same as 100nmol/L.
- beware when googling that guidelines have risen in past few years and may change again.
Deficient in D3?

- UK's Scientific Advisory Committee on Nutrition: 25% of UK over-65s have serum 25(OH)D3 below 25 nmol/L (deficit or severe deficit).
- Canada: Normal Range 75–250 nmol/L.
- SO: 25% UK seniors are at least 3-fold lower than lowest 'normal' level for Canadians.
- USA IoM guidelines recommend 100 -125 nmol/L.
Insufficiency in UK elderly

"...UK, which demonstrated that community dwelling men and women over 65 had median serum 25(OH)D concentrations of 50.5 and 43.0 nmol/L respectively"

SO roughly half of UK over-65s are not adequate, even by UK standards. And a long way short of USA-adequacy of 100 to 125 nmol/L

source: http://europepmc.org/articles/PMC5676984
How to get ADEQUATE D3
Let's set a target for serum 25(OH)D3: 100nmol/L

- within USA and Canada definition of adequacy

- How much D3 is needed, from:
  - sun
  - diet
  - supplements
  - all three sources add together.
D3 from sunlight?

Only in summer in UK. Winter sun is too weak in UVB to make D3 in the skin.

- The skin of elderly is 50% less able to make D3 from sunlight.
- Clothes and hat prevent D3 synthesis.
- SPF15 suncream prevents 99% of D3 synthesis:


SLIP..SLAP..SLOP....SUPPLEMENT
D3 from diet and supplements
How much ingested D3 is needed to reach 100nmol/L in serum?

- USA advice for adults: 2000 to 4000 IU per day (IU is International Units)
- BUT seniors absorb D3 from gut less effectively, so will be towards the higher intake requirement, ww.easy-immune-health.com/vitamin-d-absorption.html
- 2000 IU is 50 μg ( 'micrograms', 'mcg' )
- What are UK latest guidelines? .................
Public Health England advice 2016

How much vitamin D do you need?

Public Health England recently recommended that everyone takes a supplement supplying 10mcg (400 IU) vitamin D per day during autumn and winter.

This is viewed as a minimum amount to prevent deficiency diseases such as rickets and osteomalacia - bone softening in adults).

Higher intakes of 25 mcg to 50mcg vitamin D3 may be more appropriate to maintain optimum blood levels, especially in older people who have reduced dietary absorption.

- 50µg is 2000 IU – advised for the elderly
- This is lower than USA IoM recommends: 2000 to 4000 IU pd for adults.
Target D3 from diet: 50μg = 2000 IU per day

- Dietary intake of vitamin D in the UK is on average 3.7 μg = 150 IU pd
  - this is only 7% of PHE-recommended target

- Eat a whole tin of sardines every day?
  
  Sardines (~100g) canned in olive oil had....vitamin D content ....2,550 IU *

* source: //open.bu.edu/handle/2144/16849
Low fat diets and D3 deficiency

- D3 is fat-soluble so diets that avoid fat also reduce D3 intake. No D3 in plants.

[www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/]

- Vitamin D is also found in a small number of foods. Sources include: oily fish – such as salmon, sardines, herring, mackerel and fresh tuna, red meat, liver, egg yolks, fortified foods – such as most fat spreads and some breakfast cereals. In the UK, cows' milk is generally not a good source of vitamin D because it isn't fortified, as it is in some other countries.

- ........ does that add up to 2000 IU per day ?????
A capsule of 50μg D3 supplement is easy and cheap

- about 2p per day

Beware: multivitamin pills (e.g., supermarkets') usually contain minimal D content, often only 5 μg, one tenth of the PHE advice. Obviously, do not take ten multivits, buy D3 capsules!!
D3 capsules
2000 IU = 50μg

- Public Health England suggests 1 per day for the elderly (slide 40)
- PHE advice was published in 2016, earlier guidelines were lower

Amazon £15 for 600 i/c p&p
DO NOT OVERDO D3

- some supplements contain far too much D3, and are potentially toxic:
  
  [link](https://www.independent.co.uk/news/uk/home-news/health-warning-over-toxic-levels-of-vitamin-d-sold-in-supplements-a7625331.html)

- PHE: safe upper limit for serum 25(OH)D3 is 220 nmol/L

- Maybe supplement with Magnesium:
  
  [link](https://www.vitamindwiki.com/Headache+with+vitamin+D+may+mean+you+need+Magnesium)
Avoid Vitamin D2


We also found that participants who were given vitamin D2 had a substantial drop in the levels of vitamin D that your body makes naturally (that is, our vitamin D3 levels), which suggests that taking vitamin D2 may actually be harmful to the body in the long run. A large review of studies has shown that vitamin D2 and vitamin D3 have different effects on our health.

See also:


- BEWARE: some multivitamin tablets state “Vitamin D”. Best avoided as it might be D2. eg see label on slide #3
Serum D3: does 'one size fit all'? 

- Probably not. Known VDR polymorphisms.
- Sensitivity to 1,25(OH)D3 varies:
  - VitDbol study. epigenomic and genomic actions of VDR
  - found three groups with low, medium or high sensitivities, roughly 1/3rd of population in each.
- Implication of being low sensitivity with low serum D3 ????
“Am I D3 deficient?”

What are the signs?
Clues to D3 deficiency

- many signs are often attributed to 'just getting old'
- while a 2p D3-capsule per day may not restore the first flush of youth, it may be a step in the right direction............
Symptoms of deficiency of D3

GP online on D3 deficiency:

"Adults most commonly present with pain (usually in the ribs, hips, pelvis, thighs and feet) and proximal muscle weakness. More diffuse muscular aches and weakness can also occur. Lethargy is a common symptom.

- My 'proximal muscle weakness'...Feb 2016....resolved in 6 weeks with 2000 IU pd."
Clues to D3 deficiency

- alway get infections each winter: coughs, colds
- persistent cough in winter
- winter depression, irritability
- muscle weakness, 'trembling' weakness
- muscle pain lasting several days after exertion
Starting supplementing D3

- **if on any medication consult GP first.** Knowing your serum level beforehand can be useful as NHS guidance only supports a serum measurement if deficiency is suspected by GP.

- **do not expect instant results.** D3 is stored in adipose tissue and filling the stores takes weeks.

- serum D3 can take 2 to 3 months to reach the new stable higher level.

- My response to supplements:
  
  2000 IU pd raised serum 25(OH)D3 to 100 nmol/L
  
  6000 - - - - - - - - - - 170
“Slip, slap, slop” and low fat diets

Research points to possibility of epidemics in the making.

- disease may only become symptomatic after decades of poor D3, eg brain
- younger generations may be at risk now.

“Mad dogs and englishmen….. “

- wise men indeed ?
Thank you

- pdf archived on Ruthin U3A website
- can be downloaded, fwd link to family/friends
- additional slides cover magnesium deficiency
- if you read any of the cited science papers, read the Conclusions first!
- sites for science: Google Scholar or http://europepmc.org/
- Mayo clinic is good for medical backgrounds.
D3 capsules
2000 IU = 50μg

- Public Health England suggests 1 per day for the elderly (slide 40)
- This is PHE advice published in 2016, earlier guidelines were lower

Amazon £15 for 600 i/c p&p
Measure your blood D3

£28 test done through the post by a PHLS lab in Birmingham

Measure blood 25(OH)D3

Now, late winter, is best time to measure.
Magnesium deficiency

- Lay summaries of the science:
  http://www.mgwater.com/

- D3 supplementation increases Ca and Mg uptake from gut, so important to keep dietary Mg adequate. Mg deficiency seems to be widespread, but does not show in blood [Mg].

  https://www.vitamindwiki.com/Headache+with+vitamin+D+may+mean+you+need+Magnesium
Magnesium deficiency signs

- Some of the problems being experienced by those taking vitamin D are:
  - Headaches
  - Insomnia
  - Jitteriness
  - Muscle Cramps
  - Anxiety
  - Heart Palpitations
  - Constipation

- All of which are exactly the same as Signs of Magnesium Deficiency!!
Magnesium with D3

- I take 3 x 500mg Magnesium chloride tablets per day.
- this is a total of 180mg elemental Mg per day, roughly half the daily need, diet provides the remainder.
- tap-water hardness can influence Mg intake.
- see next slide
"...in order to prevent or ameliorate vascular- and cardiac-related disorders, our diets and/or drinking-water (and beverages) should be supplemented with magnesium. For the diets, the available data suggest that the total magnesium intake must be at least 450–500 mg/day, and drinking-water should contain a minimum of 25–50 mg/l (at present, in the United States, many of our potable water sources contain <10 mg/l). At the turn of the past century, we were ingesting, in the United States, about 450–500 mg of magnesium per day; at present, we are ingesting about 175–248 mg/day — thus, a considerable shortfall. Corrections of these deficits should perforce lead to healthier bodies, less cardiovascular diseases and longer lifespans."
When considering the role of \( \text{Ca}^{2+} \) in ageing, it is important to include magnesium, which is closely linked to both vitamin D and \( \text{Ca}^{2+} \). One the functions of magnesium is to enhance the synthesis of vitamin D (Rude et al. 1985; Risco & Traba, 1992; Deng et al. 2013). There are now indications that low levels of magnesium are linked to a number of diseases that are also associated with vitamin D deficiency. For example, a deficiency in magnesium has been linked to ageing. Lower magnesium levels have been found in individuals with hypertension and metabolic syndrome (Rotter et al. 2015). Low blood pressure and an increased risk of stroke have also been observed in individuals with low magnesium levels (Bain et al. 2015). Some of the actions of magnesium are mediated through a reduction in \( \text{Ca}^{2+} \) signalling processes. In the brain, extracellular magnesium can reduce \( \text{Ca}^{2+} \) entry through voltage-gated \( \text{Ca}^{2+} \) channels and NMDA receptors (Wilmott & Thompson 2013). An increase in magnesium in the brain reverses the decline in cognition in Alzheimer’s disease (Li et al. 2014). It is clear from all this evidence that magnesium plays an important role in regulating the activity of both \( \text{Ca}^{2+} \) and vitamin D.
Dr Terry Wahls, Clinical Prof Medicine, Univ Iowa

- serum 25(OH)D3:
  - Ideal target = 80ng/ml = 200 nmol/L
  - high even by USA guidelines. close to PHE safe limit
  - if take > 2000 IU pd, test urged 3 monthly until stabilised.
- for MS, also PD, Alz, dementias.

(Tks to Kay and Tom for the heads up.)
For reference: D3 on one page.
by Prof A W Norman,
Univ California Riverside.

website: http://vitamind.ucr.edu/
CONTRIBUTIONS OF VITAMIN D TO GOOD HEALTH

SKIN + UV LIGHT → KIDNEY

Vitamin D₃ → 25(OH)D₃ → 1,25(OH)₂D₃ → 25(OH)D₁α-hydroxylase

DIET → LIVER

PARACRINE

COMMENTS (at least 10 cell types)

Vitamin D itself is biologically inactive. It is a precursor of 1α,25(OH)₂D₃. Serum 25(OH)D₃ is a marker of vitamin D nutritional status. Its concentration should be 30–60 ng/ml.

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<th>SERUM 25(OH)D</th>
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<td>&lt;12</td>
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<td>5 - 10</td>
<td>12 - 25</td>
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<td>30 - 60</td>
<td>75 - 150</td>
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<td>&gt;150</td>
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PHYSIOLOGICAL SYSTEMS

- ALL CELLS
- CALCIUM HOMEOSTASIS
- IMMUNE SYSTEM
  - INNATE
  - ADAPTIVE
- PANCREAS β Cells
- HEART & CARDIOVASCULAR
- MUSCLE
- BRAIN

BIOLOGICAL RESPONSES

- Cell cycle regulation
- Cell proliferation inhibition
- Intestinal calcium absorption & Bone remodeling
- Stimulate synthesis of antimicrobial peptides
- Dendritic and T-cell function
- Facilitate insulin secretion
- Renin-angiotensin regulation, Coagulation, fibrinolysis, heart muscle function
- Promote normal skeletal muscle development; improve muscle strength
- Brain has VDR & 1α-Hydroxylase
- In progress

VITAMIN D DEFICIENCY ASSOCIATED DISEASES

- Cancer (prevention)
- Prostate, breast, colon cancer
- Leukemia(s) (treatment)
- Rickets, Osteomalacia, Osteoporosis
- Increased prevalence of infection; e.g. tuberculosis
- Increased autoimmune diseases; e.g. type 1 diabetes, multiple sclerosis, inflammatory bowel disease, psoriasis
- Impaired glucose tolerance and type-II diabetes
- High renin hypertension; increased cardiovascular risk factor; increased thrombogenesis.
- Muscle myopathy; increased falls
- Vitamin D deficiency in utero may contribute to developmental problems

Further Information

A. W. Norman
email: anthony.norman@ucr.edu

Evidence indicates that a daily vitamin D intake of 2000 – 4000 IU/day is safe and should elevate your serum 25(OH)D levels to ~40 – 50 ng/ml. Everyone should have their serum 25(OH)D levels determined at least once yearly. More vitamin D-related health information is available at both the Vitamin D Workshop website http://vitamind.ucr.edu/ and the GrassrootsHealth website http://www.grassrootshealth.net/ (2011)