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REVIEW

Vitamin D status and its management for achieving optimal health benefits in the elderly

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ABSTRACT

Introduction: Vitamin D deficiency is common, world-wide, but vitamin D repletion throughout life, and into older age, has accepted health benefits for bone. Many mechanisms through which vitamin D also benefits soft tissues are understood, and clinical evidence of such benefits is now accumulating, especially following re-analyses of trial data, which are revealing previously missed health benefits with correction of deficiency.

Areas covered: The sources of vitamin D, its activation, mechanistic effects; problems of trials of supplementation for reducing health risks, the benefits shown for mortality, cardiovascular disease, infection and cancer; the global problem of vitamin D deficiency; age-related reductions in vitamin D efficacy, and currently recommended intakes.

Expert commentary: High prevalence of vitamin D deficiency and insufficiency worldwide have proven ill-effects on health. Governmental efforts to improve population repletion by recommending minimal daily intakes does benefit some but is not effective at the population-level. However, food fortification with vitamin D3, already implemented in some countries, can solve this highly avoidable problem cost-effectively and is probably the best way to abolish vitamin D inadequacy, allowing public health benefits to emerge over time, thereby allowing future research on vitamin D to be directed at emerging issues on vitamin D.

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1. Introduction

Vitamin D deficiency is common world-wide and is a public health problem that needs to be addressed since deficiency is reported in between 30 and 80% of populations at all ages, and in tropical as well as temperate and colder countries. This review, therefore, outlines, in brief, our current understanding of the benefits to human health of adequate long-term vitamin D provision through reports of its effects on health outcomes (clinical and epidemiological data), of its 'modus operandi' (mechanistic effects), of the changes in vitamin D patho-physiology with age, and of the scale of vitamin D deficiency internationally.

1.1. Sources of vitamin D

Vitamin D_3, (cholecalciferol), synthesized by early unicellular aquatic organisms under UVB radiation (wavelength 290–-320 nm) protected them against intense UVB irradiation, is consumed up the food chain, and formed in mammalian skin by UVB-thermally-induced complexation of cholesterol-related precursors. In those living at latitudes away from the equator UVB availability is limited to the summer, more being absorbed by the atmosphere the lower the sun is in the sky so that skin D_3 synthesis is only activated between ~11 am and 3 pm in temperate climates from April/May to late September. Modern lifestyles, occlusive clothing, sunscreen use, sun hats, car travel and indoor work/exercise further reduce skin exposure to UVB, as does the increasing avoidance of exposure to sunshine for reduction in the well known risks of skin cancer, and in particular, of skin melanoma. Older people often spend longer indoors than younger, women use high sun-factor make-up to prevent 'ageing', further reducing skin exposure to UVB. Furthermore, older peoples' skin makes ~1/3 the VitD than young skin with equal doses of optimal wavelength UVB [1]. VitD precursor 7-dehydrocholesterol converts to cholecalciferol which moves into the bloodstream on carrier proteins with feed-back regulation through various pathways for cholecalciferol synthesis that avoid excessive VitD formation.

Sunshine induces vitamin D_2 (ergocalciferol) synthesis similarly from plant ergosterol, especially fungi, and foods containing fungi such as sundried cocoa beans that contain fungi, explaining why dark chocolate contains significant amounts of vitamin D_2 [2] Though $VitD_2$ cures rickets as well as $VitD_3$. Its pharmacokinetics differ and this review discusses only $VitD_3$].

Since various factors now limit skin synthesis of D_3 across most populations, people are very dependent on oral VitD intakes, but food provides only small amounts in egg yolk and most dairy products, with rather more in wild (not farmed) oily sea-fish and fortified foods, when available.

Meat contains some 25(OH)D. UK margarines are fortified in small amounts, together with some yoghurts and breakfast cereals. North America commonly fortifies milk and orange juice. In Finland, liquid dairy products and fatty spreads were fortified,

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voluntarily, [0.5 µg (20 IU)/100 ml & 10 µg (400 IU)/100 g, respectively] from December 2002, and those amounts were doubled in 2010, virtually abolishing deficiency at all ages as confirmed at audit of non-supplement users (and without toxicity in supplement-users) [3].

Elsewhere vitamin D insufficiency/deficiency remains common globally, even in tropical countries, whether or not they have officially recommended daily intakes, whether supplements are easily available or not, and elders are often the worst affected [4].

1.2. VitD absorption

VitD absorption is higher with fatty than non-fatty foods, and people should take VitD supplements with fatty foods. Gut absorption of radio-labeled cholecalciferol from standardized high fat meals, is reduced in older vs. younger adults [5]. Recent work has focused on reductions in tissue VDR expression with age, as in skeletal muscle [6], and the accompanying reductions in gut calcium absorption. Vitamin D supplements often contain calcium, confusing their specific effects. Calcium supplements can have adverse effects, whilst equivalently increased dietary intakes demonstrate beneficial effects, at least for the CVS [7].

Though inadequate performance of the vitamin D axis is reported with ageing (as above) VitD inadequacy may increase ageing processes through adverse effects on inflammation, gene structure/function, and other processes [8]. However, whether deficiency is a causal factor for increased 'ageing', or creates adverse feed-back effects, is unclear.

1.3. Vitamin D activation pathways and their homeostasis

Major physiological effects of biologically inert VitD are induced by activated (hormonal) VitD, the 1,25-dihydroxyvitamin D_3 metabolite of VitD, formed in two stages by specific cytochrome CYP450 hydroxylase enzymes. Firstly intact VitD is 25-hydroxylated by CYP2R1 and CYP27A1 enzymes in the liver, and then further hydroxylated by a specific 1,α-25-alpha-hydroxylase, forming 1,25-dihydroxyvitamin D (calcitriol; hormonal VitD), first identified in the kidneys, this activation site providing circulating calcitriol, potentiating calcium-absorption and bone calcification. Renal VitD activation increases with higher serum parathyroid hormone (PTH), falls with increased serum calcitriol and Fibroblast Growth Factor 23 (FGF23) from bony tissues, providing tight regulatory homeostasis of serum calcitriol while increased serum calcium/phosphorous suppress PTH secretion. Target tissues also activate 25-hydroxyvitamin D, through the same CYP27B1-hydroxylase, the *in situ* calcitriol produced acting locally (autocrine and paracrine effects). Regulation of calcitriol production in target tissues differs from renal regulation, as it increases with substrate availability (serum 25(OH)D) is not regulated by PTH and is reduced by increased local 24(OH)ase catabolic activity, which is induced mainly by higher calcitriol concentrations [9]. Other VitD metabolites with potentially contributory roles include C-3 epimers. Further novel and complex pathways for activation and signaling identified more recently, are under evaluation, but not discussed further in this review [10,11].

1.4. Vitamin D metabolite transport in the circulation

Intact VitD clears rapidly from the circulation, as does calcitriol – making serum calcitriol data unsuitable for assessing VitD repletion. Circulating 25(OH)D is mainly bound to VitD binding proteins (DBPs) from the liver and other plasma proteins, giving bound serum 25(OH)D clearance a half time of ~2 weeks, so that it is used to assess VitD status. This complex is absorbed into renal tubules though megalin/cubulin cell surface protein complexes [12].

1.5. Mechanisms of action of vitamin D on target tissues – endocrine, autocrine and paracrine

Genomic effects follow binding, of VDR heterodimers with retinoid-X receptors (RXRs), to

VitD response elements (VDREs) in promoter regions of several thousand genes, ± other

associated transcription factors [13].

Rapid non-genomic effects, identified as explaining calcium absorption, commonly follow VDR binding to rapid response-binding proteins within cell wall caveolae (lipid rafts), activating calcium ion-channels [14]. Classical physiological effects relevant to bone are achieved through effects increasing calcium absorption, and modulating bone metabolism.

Physiological effects on non-bony tissues are achieved similarly, by rapid non-genomic activation of calcium ion channels, increasing intracellular calcium concentration, or through slower genomic effects.

1.6. Epigenetic effects of vitamin D modulate gene expression

Epigenetic effects of vitamin D modulate gene expression, (e.g. gene silencing), alter gene expression through DNA methylation or RNA modifying histone deacetylation without changing DNA base sequences and many persist into later life. While such changes are important [15], and are likely to be protective against early fetal loss, maternal deficiency in pregnancy reduces these epigenetic effects, which has many known adverse effects on offspring in later life, likely increasing osteoporosis risks with ageing and also the risks of multiple sclerosis and CVD [16,17].

Further physiological effects modulated by mechanisms affecting inflammation, auto-immunity, infection and cancer risks are discussed elsewhere.

2. Tissue and metabolic changes with ageing, relevant to the vitamin D axis

Reductions with age are found in VitD synthesis, VDR expression, gut calcium absorption, VitD absorption, and renal VitD activation, with reduced calcitriol production during PTH infusions in older people [18], increasing the risks of VitD deficiency with age.

Structural integrity of genes is provided by tandem-repeat DNA sequences (telomeres), at eukaryotic chromosome tips that shorten with each cell division, and thus with age. Increased telomere loss in length is seen in degenerative

disorders, with increased telomerase enzyme activity, which is inhibited by calcitriol [19]. Telomere length correlates directly with VitD status and supplementation reduces telomere shortening rates, experimentally; whether Vit-D can preserve telomere length in ageing by long-term DNA stabilization is unknown [20-23]. In addition, the clearance of pathogens and abnormal or damaged cell components/cells by macrophages, (autophagy), as in inflammation, and apoptosis (self-induced cell-death, as in adipocytes and cancer cells) are enhanced by calcitriol experimentally. Thus, VitD repletion contributes to tissue health, and has the potential to reduce cancer risks, life-long [23].

3. Associations of vitamin D status with disease and health outcomes with correction of deficiency

The best known associations of lack of vitamin D are with bony disorders, including childhood rickets, adult osteomalacia and worsening of osteoporosis, but major associations with general health, with survival and with many non-bony disorders have emerged over recent decades.

3.1. Overall and cardiovascular mortality rates

Higher vitamin D status is associated with reduced age-adjusted mortality rates prospectively, and, increasingly also, in randomized controlled trial (RCT) findings across all adult age groups. In > 11,000 adult community residents in Minnesota, USA, White subjects with baseline 25(OH)D values <50 nmol/l] showed increased overall mortality over ~5 years and HRs fell dose-wise with increasing baseline D status (peaking at x 2.6 fold in those with the lowest vs. those with the highest baseline D status] [24]. Australia had similar findings from record-linkage data in a prospective 20-year community-based cohort study of 3946 people aged 25–84 years (1994/5 Busselton Health Survey) with 889 deaths [363 from cardiovascular disease [CVD] & 944 CVD events [242, heart failure], HR = 0.83 for each SD-sized increment in baseline D status [95% CI, 0.77–0.90] in CVD/heart failure deaths, but not in non-fatal CVD 'events': greater mortality risks were seen with baseline 25(OH)D values <65 and <55 nmol/l for overall CVD or heart failure mortality respectively, and not affected by diagnosed CVD at baseline [25] suggesting that repletion is worthwhile, even with overt CVD.

3.1.1. Cardiovascular disease

VitD improves skeletal muscle strength, with evidence for myocardial benefits. Supplementing 43 patients, [16 aged >50 years], with severe dilated cardiomyopathy already on optimal medication, [25(OH)D < 50nmol/l], at 200,000 IU/week over 12 weeks improved 6 min walking distance by ~150 ft, (validated by serum pro-BNP values reducing from 1024(± 635) to 159(± 80)pg/mL [$p < 0.005$]) [26]. Recent meta-analysis of RCT data has reinforced these findings, showing that 10–20 µg VitD/day in deficiency reduced both all-cause and cancer-related mortality in middle-aged and older people [27]. Convincing reductions in mortality, respiratory infections and asthma exacerbations were demonstrated in another recent RCT-meta-analysis [28], those authors suggesting that older meta-analyses had often used data of dubious quality, used RCT data directed at bony endpoints, or without baseline VitD status, and they also suggested that future reviews/meta-analyses should ensure that RCTs were matched, and adequate in design, to improve meta-analysis quality (see section on RCTs).

Atheromatous disease of large blood vessels begins in childhood and is progressive, fatty endothelial deposits (plaque) enlarge, fibrose and narrow arterial lumens, and become unstable due to inflammation and foamy macrophage infiltration, with increased risks of plaque breakdown, overlying clot formation, and precipitation of arterial occlusion (myocardial infarction, ischemic stroke or peripheral gangrene). VitD status modulates factors aggravating these processes, and the vasculature, like the myocardium, is a VitD target tissue [29,30]. VitD increases both myocardial contractility, through VDR-dependent increases in myocyte calcium current transients, and vascular smooth muscle function, while VitD status independently predicts coronary artery disease severity. [31,32]

Plaque breakdown risk by tissue destructive matrix metallo proteinases (MMPs) (especially MMPs 2/9), increases with macrophage infiltration, simulating efforts to develop anti-MMP Drugs [33]. However, modest oral VitD supplementation of healthy, though VitD inadequate subjects, reduced plasma MMPs (MMP-9 by −69%), where baseline plasma MMP-9 had been inversely associated with VitD status [34], an effect now well established in vascular and other tissues. Thus, long-term VitD repletion should contribute cost-effective protection against plaque instability, as well as inflammatory damage, long-term, which is also suppressed by VitD; supplementation (>1000 IU/day) suppressing pro-inflammatory cytokine production (e.g. IL-6), especially in older women, at 25(OH)D values ≥80nmol/l [35]. VitD status is also associated inversely with proinflammatory markers, and total 25(OH)D is a better risk marker than free 25(OH)D, or raised IL-6, in older men [36]. VitD additionally promotes anti-inflammatory cytokine secretion, (e.g. of IL-4 and IL-10) [37]. Thus, long-term VitD repletion offers at least two proven effects protective for cardiovascular health, while low VitD status also marks increased wall stress and myocardial damage, potentially providing additional benefits with supplementation [38].

Community-dwelling patients aged >65 years with cardiac hypertrophy, muscle wasting, VitD deficiency, and raised serum PTH, had raised circulating Fetuin-A levels, correlated with serum PTH, possibly protective since Fetuin-A inhibits vascular calcification [39]. However, increased arterial wall stiffness in older populations is worsened with VitD inadequacy, and varies with other vitamins, so that their potential for interacting requires clarification [40,41]. Further complexity in assessing the value of VitD for vascular protection arises since not all plaques are 'rupture-prone'. Vulnerable plaque identification remains under development [42]; and whether vulnerable plaque rates will vary with VitD status, and/or fall with supplementation, will be of interest.

3.2. Metabolic syndrome (syndrome 'X')

In 1988, the concept of a 'syndrome' based on increased insulin resistance (IR) [later called metabolic syndrome (MetS)] was proposed, (based on associations of IR with increased insulin

secretion, hypertension, dyslipidemia, obesity, hyperglycemia, and increased CVD risks), and where inadequate compensatory insulin secretion and beta cell dedifferentiation lead to T2DM [43,44]. The author, whilst working on VitD, noted reports of seasonal variations for each aspect of MetS, with lower risks summer than winter, suggesting a role for hypovitaminosis D in MetS development [45], though varying UVB radiation may contribute to these variations directly in other ways [46,47].

3.3. Insulin resistance

IR is commonly raised, dose-wise, with lower VitD status [48]. In an early RCT of vitamin D, when baseline 25(OH)D was raised to ≥80nmol/l over 6 months in normoglycemic subjects, IR was reduced [49]. This effect is now confirmed by large meta-analyses of two RCTs, one that showed reductions in IR in T2DM patients with increased VitD status, and the other showing reduced T2DM risk in initially normoglycemic subjects given VitD (2000 IU/day), especially when VitD was given without calcium supplements, those risk reductions increasing dose-wise the lower the baseline VitD status, though meta-analysis of the data without baseline VitD status stratification showed no evidence of benefit [50,51].

3.4. Obesity

Obesity and circulating 25(OH)D concentrations are inversely related, probably reflecting increased distribution volumes since a large bidirectional Mendelian randomization analysis suggested obesity reduced 25(OH)D values but that obesity was not reduced by higher vitamin D status [52]. Furthermore, weight loss usually increases serum 25(OH)D, but is not induced by supplementation, and the supplemental dosages needed to raise VitD status are increased in overweight and obesity. Adiposity increases circulating inflammatory cytokines, with adverse effects remotely, (e.g. on the CVS). Early life repletion can reduce later adiposity, while later-life repletion does not, though it reduces some associated risks [53].

3.5. Hypertension

Summer blood pressure (BP) reductions, and inverse associations of BP with VitD status could be explained by the suppression of renin secretion [and hence of the renin angiotensin system (RAS)] by VitD [54], and also by the increased vasodilatation induced by UVB-related increases in skin nitric oxide (NO), and the increased vascular reactivity found with VitD supplementation [55–57]. BP reduction with short-term RCT supplementation is rare [58], but has been found in younger subjects whose vessels should be less stiff [59].

3.6. Dyslipidemia

Calcitriol inhibits synthesis of long-chain fatty acids (FFAs, that form triacylglycerides) by down-regulating an FFA elongase enzyme [60]. VitD status associates inversely with atherogenic lipid profiles while supplemental RCTs show few consistent benefits, and, though circulating triacylglycerides often fall, HDL-C and LDL-C rarely improve [61–63].

3.7. Non-alcoholic fatty liver disease (NAFLD)

VitD status associates inversely with NAFLD-steatosis [64–66]. Experimentally, calcitriol reduces hepatic-triacylglyceride synthesis, steatosis, and glucose output [67,68]. However, neither observational studies nor available RCTs data suggest that VitD status affects liver fibrosis severity [69]. Additionally, liver damage may reduce 25(OH)D synthesis, confounding such studies and also acting as a vicious circle worsening MetS disorders.

4. Hyperglycemia and T2DM

Hypovitaminosis D is associated with hyperglycemia and risks of MetS and T2DM dose-wise in cross-sectional and prospective studies. Dysglycemia and dyslipidemia were present 20 years before T2DM diagnoses in 296,428 people in the Swedish AMOSIS cohort, (incident T2DM cases, 22,244) [70], confirming the long run-in for MetS abnormalities before T2DM diagnosis. Experimentally, VitD is necessary for normal insulin secretory responses to hyperglycemia, both phase 1 (rapid release of stored insulin following increased intracellular calcium) and phase 2 secretion (following insulin gene upregulation) [71,72].

4.1. Immunity – innate

Innate, (non-specific), immunity provides immediately available protective mechanisms against external insults like infections, (viral or bacterial), and foreign substances in blood or tissues by mechanisms including immune cell recruitment to affected areas through cytokine release, promoting local inflammation, complement system activation, white cell phagocytosis of dead cells and foreign matter and it contributes to activation of adaptive immune mechanisms. VitD contributes to these defences in several ways, by increasing cathelecidin (IL-37) secretion [a bactericidal and viricidal protein killing pathogens] and by modulating various helper T cell responses [37,73,74]. These mechanisms also suppress adverse effects of inappropriately prolonged immune responses [75], and are likely to contribute to health benefits seen with better VitD status, including mortality reduction in critical illness [76] and to the 'adjunctive' benefits found for VitD supplementation in managing tuberculosis, though those can vary with VDR genotype [77,78].

4.2. Immunity – adaptive

Adaptive (acquired) immunity provides additional defenses against specific external insults, (infective agents and allergens), through complex immunological responses leading to specific antibody formation against pathogens, through recruitment of dendritic cells, enhancing antibody responses to provide specific long-term protection against pathogens by rapid re-activation with re-exposure to the insult. These effects provide the basis for immunization programs against

increasing numbers of infections. Allergies develop however, when this system is activated by what would normally be harmless materials, e.g. pollen or foodstuffs [79,80].

4.3. Autoimmune disease

Autoimmune disease reflects mal-adaptive immune responses to normal tissue components, leading to on-going tissue damage, (autoimmune disease). Common examples include Type 1 diabetes (T1DM), and auto-immune thyroiditis. VitD has many effects that are protective against such disorders [81,82]. In T1DM, adequate supplies of vitamin D to mothers, infants and young children were associated with reduced risks of childhood T1DM in several studies [83–86]; T1DM is less common in older than in younger people, with increases in incidence at higher latitudes. Though various genetic factors are associated with T1DM, most causation is environmental, and early-life VitD deficiency is a contributory factor [87]. In Finland, where childhood T1DM had increased relentlessly for decades, VitD food fortification began in December 2002 and 3 years after being increased in 2010, T1DM incidence plateaued, but whether T1DM incidence in older Finnish people will also fall, remains to be seen [88].

Auto immune thyroiditis, sometimes with an initial overactive phase, and commonly leading to permanent hypothyroidism, increases in incidence with age, Chinese data shows higher rates of deficiency in patients with Hashimoto's thyroiditis or Graves disease (thyrotoxicosis) vs. Controls (76 and 70% vs. 20%), but data for effects of supplementation on rates of autoimmune thyroid diseases are limited [89,90].

Vitamin D also has beneficial effects on several aspects of inflammation, suppressing excessive responses and promoting effects protective against infection, that are active at all ages, mechanistically, and *in vivo* in humans[91]. Those with chronic diseases, including CVD, had different lymphocyte subtype patterns from those of healthy subjects amongst >8000 Chinese subjects, the patterns associated with T2DM+ deficiency suggesting Th1 lymphocyte profile induction [92]. If confirmed, this would support a contribution from pathogen-induced immune responses to the islet damage in T2DM, as well as in T1DM.

5. Neurological disorders

VDRs are present in adult neurons and supportive glial tissues. Associations are reported between low VitD status and cognitive disorders, and VitD has essential roles in early-life neurodevelopment [93], and protects the vasculature. Thus, unsurprisingly, deficiency is associated with dementia risks (both micro-vascular and degenerative), other neuropsychiatric disorders and the autoimmune disorder, multiple sclerosis (MS) [94]. MS is rare *de novo* in the elderly but damage from earlier episodes often persists. Cognitive decline increases with low VitD status, and is more common with 25(OH)Ds <20 ng/ml [95]. Greater dementia risks, structural brain damage in dementia, and worsened cognitive decline, were found prospectively with baseline 25(OH)D values <25 nmol/l [96]. Some RCTs suggest potential cognitive improvement with supplementation, and deficiency may be associated with Parkinson's disease risk [97], but these findings clearly require further investigation.

5.1. Vascular dementia

This common disorder of older-age follows multiple small cerebral infarcts (see 'cardiovascular disease'), and the benefits of life-long VitD repletion for the vasculature should extend to this form of dementia.

5.2. Alzheimer's disease

This less common cause of neuronal degeneration, disruption of cerebral white matter and neurofibrillary tangle formation has many suspected causes. Meta-analysis of available data for potential nutritional risk factors suggests that VitD deficiency increases risks of all-cause cognitive dysfunction. Though U-shaped associations were suspected in the very oldest subjects, this could well reflect the onset of supplementation with full-time care [97,98]. Inverse associations between D status and Alzheimer's disease risk are suggested, but that evidence is disputed. However, Mendelian randomization study-data shows associations between single-nucleotide polymorphisms predictive of 25(OH)D values and Alzheimer's risk (RR = 1.25 [95% CI 1.03, 1.51) [99]. A recent Meta-analysis reported significantly lower risks of dementia and Alzheimer's disease prospectively with higher baseline 25(OH)D values, dose-wise up to 35 nmol/l, but had insufficient data to look for possible effects of higher 25(OH)D values [100]. Therefore, though certainty is not available, long-term avoidance of deficiency, clearly desirable on other grounds, may prove to reduce Alzheimer's risks.

5.3. Depression and schizophrenia

Literature reviews (1995–2017) show consistent associations if these mental health problems with VitD deficiency, as for dementia of any cause, but has found no definitive evidence of causality [101]. Since ill health, physical or mental, often makes self-care difficult, especially in the elderly, it is also likely that these data reflect reverse causation from poor nutrition.

5.4. Herpes zoster

Herpes zoster (HZ), ± post-herpetic neuralgia, is painful and disabling. Protective immunization for risk-reduction is offered to older people in many countries and VitD status associates directly with better immunity to HZ in immuno-compromised patients [102,103]. Whether correcting deficiency could reduce HZ incidence, HZ relapse rates, or improve immune responses to HZ vaccination in elders in unclear.

6. Urinary tract

Oral supplementation (20,000 IU/week vs. placebo) in 511 adults ~halved urinary tract infection rates (UTIs) over 5 years, mainly in men [104]. VitD (20,000 IU × 2/week vs. standard doses) in an osteoporosis RCT on 297 postmenopausal women, over 1 year, left UTI rates unchanged, but had a novel secondary effect of reducing incontinence risk during an UTI, ($p < 0.05$) [105]. Other urinary tract associations include increases in aggressive prostatic tumor risks in deficient men [106], and VDR expression was reduced in areas of

histologically abnormal prostate in older subjects with deficiency, independent of variations in androgen secretion [107].

7. Incident hypercalcemia or hypocalcemia require medical care

Well-known causes of hypercalcemia include primary hyperparathyroidism (common in older women), bony metastases, and target tissue over-activation of VitD (in sarcoidosis and rare lymphatic disorders). Hypervitaminosis-D is rare, but correcting deficiency in undiagnosed primary hyperparathyroidism can precipitate hypercalcemia. Manufacturing errors have caused accidental over-dosage, but most recent cases have followed inappropriately high self-supplementation [108]. Hypocalcemia in older people is often 'Endocrine' in origin, e.g. hypoparathyroidism following thyroid surgery, or parathyroid tumor removal with either hyperparathryoid bone disease or with severe untreated VitD deficiency.

8. Clinical disorders affecting vitamin D metabolism

These require routine medical management, sometimes using VitD 'pharmacologically' and are outside the remit of this review. Briefly, those illuminating the roles of the VitD axis include fat malabsorption, for any reason, including bariatric surgery. Uremia reduces renal calcitriol production and leads to renal bone disease, (± osteomalacia), that requires avoidance through medical management; muscle weakness increases in uremia as do MetS risks, while features of MetS can be ameliorated, (or reversed) by VitD; thus, adequate VitD intakes for providing 25(OH)D substrate to soft-tissues and calcitriol/calcitriol analogues for bone health are commonly used in uremia [109,110]. Non-alcoholic fatty liver disease and obesity are associated with VitD deficiency, already discussed, requiring increased intakes and many antiepileptic drugs interfere with VitD hydroxylation [111]. Statin-related muscle fatigue has been improved by VitD supplementation, despite statins being suggested to be calcitriol analogues, possibly activating VDRs, (as recently demonstrated experimentally) [112–114]. Thus, VitD deficiency should be avoided in statin-users, especially since serial 25(OH)D data on 646 subjects aged >60 years in RCTs of VitD for 1 year, in 3 matched groups (17.5% taking statins, 65% deficient and with comparable baseline VitD status) showed 25(OH)D rose ~21% less in statin users than non-users (adjusted for BMI and season) [115], though whether that finding reflects reduced absorption or better target tissue 25(OH)D take up in statin users is unclear.

9. Respiratory system

VitD supplementation (4000 IU/day) reduced respiratory tract infection risks in Swedish people aged <75 years (RR = 0.64;95% CI, 0.43–0.94) [116]. Reanalysis of inconclusive RCT outcome data for rates and duration of upper respiratory tract infections (URTIs) in large numbers of community-dwellers using baseline VitD status data (Individual Participant Data) revealed significant reductions in URTI infection rates, HR = 0.88;95% CI, 0.81–0.96] overall, but HR = 0.3 (95% CI, 0.17–0.53) in those with baseline deficiency (serum 25 (OH)D < 25 nmol/l) [117].

In 107 people, aged >60 years, long-term care-home residents in the US, an average of 4.3 years on oral VitD (100,000 IU/month) in a RCT vs. controls on placebo (and on 'usual'400–1000 IU/day), giving 12,000 IU/month, revealed reductions in acute respiratory infections [RR = 0.6 [95% CI, 0.38–0.8]], and also, though falls increased in the high-dose group, fracture rates were unaffected [118].

Similar benefits have emerged from some RCTs of supplementation for acute asthma exacerbations, not always limited to those with marked baseline deficiency [119], but those data were on younger people, and further information is awaited for asthma in older people.

COPD exacerbations were reduced by supplementation in baseline deficiency (serum 25(OH)D < 50 nmol/l), but not with higher baseline 25(OH)Ds (>50 nmol/l) in smaller numbers of adults, but acute URTI rates were unaltered [120].

10. Cancer risks in adults

Mechanistically calcitriol suppresses many processes during cancer development and risks of some common cancers, (e.g. colon, breast) are associated with low VitD status. Early RCTs of supplementation were negative though one 4-year RCT of calcium (1400–1500mg/day) ± VitD (1100 IU/day vs. placebo) in 1179 female community-dwellers aged > 55 years found reduced cancer risks for combined supplementation [HR, = 0.402[95%CI,09–0.6]] but no benefit in those on calcium alone [121]. Pooling prospective and trial data in another study showed that higher baseline VitD status (≥40 ng/ml) amongst 2304 adult women aged >55 years showed reduced age-adjusted cancer risks vs. those with low baseline status [<20 ng/ml], [HR = 0.33[95%CI 0.12–0.9]] [122]. Later literature review and meta-analysis of 3 further RCTs showed reductions in incidence, and longer survival, with supplementation in breast, colorectal, lung, ovarian, and prostate cancers [123]. Thus long-term maintenance of repletion can be expected be lead to reductions in several cancer risks.

11. Major genetic disorders of vitD metabolism

Major genetic disorders of VitD metabolism manifest throughout life, often causing VitD resistance, but their management requires specialist care and is not discussed further. However, vitamin D axis gene polymorphisms that are associated with variations in function of those genes are reported, and their prevalence often varies with Ethnicity, so that these factors require inclusion in the data for evaluating findings on vitamin D from both clinical, epidemiological and mechanistic research data [124].

12. Osteoporosis, falls, fractures and muscular weakness

Falls and fragility fracture risks associated with osteoporosis increase with age, reductions in physical activity and muscle weakness, and in association with VitD deficiency, and impose large, and costly, demands on health services due to their serious

effects on later health, reducing independence and life expectancy, and increasing residential care needs. Human muscle VDR expression falls with age, as mentioned, and muscle expresses VitD activating hydroxylase, though muscle strength related more to serum calcitriol than to 25(OH)D, while both metabolites were affected by relevant genetic factors in 116 healthy volunteers aged 20–74 years [125,126]. Meanwhile, an RCT on 725 nursing home residents reported fall reductions with supplementation [800 IU/day vs. placebo for 5 months [HR 0.72[95% CI, 0.11–0.75]] while falls increased in controls [127]. By 2011, causality for increased risks of falls and fractures in VitD deficiency was generally accepted, Also, large oral interval dosing, or moderate dosing with added 25(OH)D, increased fall rates vs. cholecalciferol alone (24,000 IU/month) [128]. Optimal prevention, reported with 25(OH)D values ≥75 nmol/L, was reached by only ~50% of subjects given 800–1000 IU/day, providing further evidence that IOM recommended intakes for older adults are inadequate, so that revised guidelines are clearly necessary. Further support is provided by an RCT (4000 IU/day for 4 months in 21 disabled women aged >65 years; baseline 25(OH)Ds 22.5–60 nmol/l), where 25(OH)D increases correlated strongly with % increases in intranuclear-VDR in thigh muscle, mainly in type ll fibers, and with muscle fiber cross-sectional area increases, (averaging 10%), matching the increases in muscle strength reported with correction of VitD deficiency [129]. Furthermore, increasing supplementation of post menopausal women, up to 2000 IU/day, achieved 25(OH)Ds averaging 95.5nmol/l, reduced bone calcium flux dose-wise (by tracer- calcium studies), and increased bone calcium retention dose-wise [130].Progressive muscle mass reduction with VtD inadequacy is also seen in obesity, with muscle fat infiltration. Obesity reduces serum 25(OH)D, dose-wise, likely reflecting its dilution into enlarged fat masses (see above). Thus any adverse effects of obesity on muscle will be aggravated by associated reductions in VitD status; causing a vicious circle reducing the ability to exercise unless adequate supplementation is ensured, while the amounts of VitD needed to achieve target 25(OH)D values by overweight/obese subjects are x~1.5 and x~2.0, respectively, of intakes needed with normal weight [131]. Thus, older obese subjects will need larger daily intakes for protection of musculo-skeletal health than the increased intake recommendations currently expected from the IOM.

Meanwhile ensuring continuous VitD repletion over the lifespan is a simple and cost-effective public health option for improving bone health in elders that would greatly reduce healthcare costs. Efforts to reduce fracture risk normally include maintaining physical activity; however, in >14,600 people in the EPIC-Norfolk Cohort study aged 42–82 years over ~15 years, VitD status predicted 30% of fracture risks (adjusted for other risk factors including smoking and obesity), but baseline physical activity assessment was not a predictor [132]. Further studies using serial assessments of obesity, VitD status and physical activity could prove to be more informative.

13. Oral health and vitamin D

Dental plaque severity associates inversely with dairy food intake in older adults with higher, but not lower, VitD intakes [133]. Animals with activating hydroxylase gene-knock-out on normal rodent chow showed increased alveolar bone loss and degenerative changes in periodontal tissues, with higher tissue destructive MMP content, than are seen with ageing [134]. Thus vitamin D repletion should contribute to protection against periodontitis, associated tooth loss, as well as acute gum infections.

14. Interactions of vitamin D with other nutrients and environmental risk factors for chronic diseases [e.g. vitamin A, magnesium, cucurmin, areca catechu (betel quid) chewing and smoking]

Vitamin A provides retinol-receptor ligands and excessive intakes reduce VitD efficacy in animals. Excessive Vitamin A intakes, common in prosperous countries, increased osteoporosis and fragility fracture risks in women, and blocked RCT evidence of VitD supplement-induced reductions of lung tumor risks [135–137]. Magnesium (Mg) is a co-factor for many enzyme systems including VitD activation, and Mg deficiency increases bony and non- bony risks associated with VitD deficiency, including MetS and CVD. As the 4th most abundant mineral in the body, adequate intakes are required lifelong, but they have fallen with intensive farming and altered eating habits [138]. Antacids often contain MgOH, but Mg is poorly absorbed, and Mg-rich foods are expensive, and/or unpopular (e.g. almonds, sesame seeds, broccoli, green leafy vegetables, brown rice, tofu, whole grain foods and oatmeal). Mg supplementation is used therapeutically, but increasing population-level Mg intakes will probably require food fortification [139]. Cucurmin (in turmeric) activates VDRs, possibly accounting for its many health benefits, including reduction in colon-cancer risk, and its consumption may confound RCTs [140]. Life-long avoidance of smoking benefits elderly health, reducing risks of osteoporosis, fragility fractures and lung cancer risks. Smoking reduces PTH responses to hypovitaminosis-D, and independently predicts MetS, and this effect may aggravate smoking risks, as it does for osteoporosis risks (possibly through reduced renal calcitriol synthesis) [141]. Betel-quid (*Areca catechu* nut) chewing increases MetS risk, including its sequelae, and paternal chewing increases never-chewing offspring MetS risks, dose-wise, (those risks falling over time after habit cessation) [142,143]. This habit may confound studies on VitD and health in any betel-using population, and the habit is currently used by ~10% of the global population (~700 million people). Furthermore, chewers PBMCs show dose-wise increases in VitD-catabolic 24-OHase expression with parallel reductions in serum calcitriol, potentially aggravating VitD inadequacy through generally reduced calcitriol production [144].

15. Vitamin D deficiency and its prevention in elders

VitD medication for newly diagnosed, or long-term disorders, requiring continuing medical supervision is not discussed. Definitions of deficiency and repletion in healthy people 'set' using serum 25(OH)D concentrations derived from various studies on bone health, vary considerably, with values <30 nmol/l set by the North American Institute of Medicine (IOM), and <20 nmol/l in the UK.

15.1. Serum 25(OH)D 'cut-offs' for insufficiency

Intakes advised to avoid bony and non-bony risks vary, as do recommended 'cut-offs', the IOM and American Endocrine Society setting >50nmol/l for bone and >75–125 nmol/l for soft tissues [145], with a recommended upper limit of 125–-150 nmol/l, though values up to 250 nmol/l were safe on 10,000 IU/day for a year [146]. Bone depends on tightly regulated circulating calcitriol concentrations, but soft-tissues probably depend largely on locally produced calcitriol, in turn dependent on available serum 25(OH)D, thus different 'status' requirements may well be found between those for bone and for different soft-tissues.

15.2. Current minimal daily VitD intake recommendations for elders

Current minimal daily VitD intake recommendations for elders vary between countries, at 800 IU/day aged >71 years in Canada, 600 IU/day for older adults in the US (IOM and NIH advice), (ods.od.nih.gov> factsheets> vit –), at 600 IU/day at all ages by the European Food Safety Agency (www.fda.europa.eu.topics); at 400 IU/day in the UK for everyone aged >1 year old throughout the winter months (October to late March/early April), but all year round for those 'at risk' of VitD insufficiency (elders, those in residential care, housebound, wearing covered-up clothing, with dark skin or living indoor lives)(www.nhs.uk/new/food-and-diet/; 21/07/18), while WHO and European recommendations for older people range between 400–600 IU/day for >66 year olds. Intake recommendations from the American Endocrine Society for healthy adults are 600 IU/daily, increasing to 800 IU/day for people >70 years old. The international federation on osteoporosis advises 600 IU/day for healthy people aged 19–70 years and 800 IU/day if aged >70 years [147], while calcium intakes of 1000–1200 mg/day are advised for women >51 and men >70 years old. Most advisory bodies currently advise against VitD intakes >4000 IU/day. In addition, supplementation with 25(OH)D itself (at 10–15 microg/day) in people >65 years old achieves stable increases in serum 25(OH)D safely, but is unlikely to be suitable, or affordable, for population-level repletion [148]. Whether the guideline intakes suggested are adequate, or taking them achieves the desired target status, is doubtful and needs to be checked, but unfortunately the necessary audits are rarely performed, though food quality checks on vitamin content are usually routine.

15.3. Recent IOM intake guidance underestimated requirements

This arose from calculating intakes for achieving target status on average rather than in the 97.5%, of the population aimed for [149,150]. so that increased IOM guidelines (by × 7–10 fold) are urgently needed. One RCT in 305 people > 65 years old supports the significance of that miscalculation, since intakes of 4000 IU/day achieved a mean 25(OH)D of 137nmol/l, within the IOM target range of >90 nmol/l, but only reached >90 nmol/l in 88% of subjects, supporting the need for much increased intake recommendations for older people [151]. Studies of population-level self-supplementation are rare. VitD status is increased in residential care homes by UVB lamps, but this is impractical. Other studies on oral supplementation suggest that the intakes advised for elders at especial risk of deficiency should be adequate for housebound adults [152]. However, the supplements offered are often unacceptable, especially when containing calcium, which can cause gut discomfort.

16. Role of food fortification

This voluntary measure was introduced in Finland in December 2002, and doubled in 2010, after which audit showed virtual eradication of deficiency at all ages, and Finland's continuously increasing incidence of childhood T1DM in Finland plateaued 3 years later [88]. Hopefully, similar reductions in other diseases associated with hypovitaminosis D may also appear over time.

17. Recommended calcium intakes for adults

Calcium intakes are as important for bone health in older as in younger adults and intakes of at least 1000 mg daily are usually advised. Calcium is probably best obtained from food, (dairy products or hard water), since calcium supplements may have adverse CVS effects in post-menopausal women [7]. Whilst the US Preventative Services Task Force Recommendation Statement of 2018 reported no convincing benefits of calcium or VitD supplementation, or both, in community dwellers, American populations are probably better supplied with these nutrients than people in many other countries. Thus, where adequate intakes of calcium and/or VitD are not provided by available diets, food fortification with both these nutrients should be considered.

18. Prevalence of vitamin D inadequacy in older people

Rates of VitD deficiency and insufficiency are high in older populations of all ethnicities at higher latitudes in Europe and the USA; though less high where food fortification is used (North America and Finland). Prevalences of deficiency/insufficiency were 5–67% and 17–87%, respectively, in a review of population-based/representative sampling data between 2004 and 2014, covering sub–tropical and southern European countries. [153–161] Deficiency is well recognized to be increasingly common, and more severe, with loss of independence, becoming housebound or moving into residential care. Immigrants with dark skin into countries at northern latitudes have high risks of VitD inadequacy, especially women wearing covered-up clothing. Older south Asian men may have improved status through assuming domestic roles with early retirement, including shopping, and wearing short sleeved shirts in warm weather.

18.1. Assessment of vitamin D repletion (status) in older people

Serum 25(OH)D concentrations are used as at other ages. Validated questionnaires are effective in assessing VitD intakes

in older, as in younger, people [159]. Serum calcitriol content is not normally used as it is tightly regulated, has a short half life, and serum levels are steady, or even rise, in deficiency unless it is extremely severe. Similarly, serum PTH increases in deficiency, but associates loosely with serum 25(OH)D, making cut-offs for defining repletion unreliable. Advice on VitD intakes can be given without assay data unless some medical condition requires it. 25(OH)D assays are, however, needed for audit of population VitD status audit, for research on VitD status in relation to health outcomes and for RCT outcome assessment. Many ethnic groups are reluctant to provide blood samples, and samples only provide momentary data for status, while serum 25(OH)D fluctuates with season, diet and supplement usage, both in healthy people, and in non-supplemented elderly people admitted acutely to hospital [160]. Serum 25(OH)D content classically peaks, and bottoms-out, some weeks after the highs and lows of summer and winter UVB, these slow changes reflecting 25(OH)D binding to specific circulating VitD binding-proteins (the DBPs) and to other serum proteins. Difficulties posed by 25(OH)D assay data include variation between findings with different assays, especially immunoassays. Early 25(OH)D_3 assay data also suffered from cross-sensitivity to 25(OH)D_2, whose biological efficacy is similar to 25(OH)D_3, but which has different pharmacokinetics; newer methods assay both metabolites, allowing clarity to develop on this matter. Existing data, however, suggests that cholecalciferol can be more effective than ergocalciferol, but vegans refusing animal cholecalciferol will accept ergocalciferol. The use of more reproducible HPLC-Tandem Mass Spectroscopy methodology, and of international standards and controls, has reduced these problems, and, for comparisons of VitD status over time, between studies, and during RCTs, older and newer assay data can now be 'harmonized' since stored samples can be re-assayed for data adjustment, since 25(OH)D remains intact, when stored in the dark, for over 20 years; this 25(OH)D stability also allows 25(OH)D assays on dried neonatal blood spots [161,162] for studying associations of early-life VitD status with later health risk since the loss of the normal epigenetic effects of VitD in the fetus in maternal deficiency persist into later life. Despite these problems, one study reported that 25(OH)D values predicted ~50% of 25(OH)D in samples taken after 14 years, which has helped with follow-up studies when no stored samples were available for re-assay [163].

Consistently significant associations of serum 25(OH)D with health outcomes are reported in observational and prospective studies, and 25(OH)D data are invaluable for re-analyzing RCT data stratified by individual baseline status, where correcting deficiency is increasingly revealing beneficial effects missed on earlier analyses [117,164].

Free (unbound) 25(OH)D may be biologically important and may be a more important substrate for some target tissues than others, thus, further understanding of the roles of free 25 (OH)D and other recently identified VitD metabolites circulating at low concentrations is awaited [165].

19. Randomized controlled trials

Potential benefits of VitD supplementation for acute disorders are easier to examine in RCTs than those for chronic disorders. Meta-analysis of RCT data shows that overall mortality is reduced by supplementation, and acute illnesses (colds, 'flu and asthma exacerbations) are reduced by supplementation [28] However, if prospective study data means anything, reductions in T2DM, CVD, MI, and BHT, risks, all likely to have been present long before diagnosis, should reduce with supplementation, but only if it begins early enough in disease development, (*e.g. CVD begins in childhood and T2DM develops after >10 years of increased IR*), and is maintained over many years or decades, making worthwhile RCTs difficult and unaffordable, and the use of unsupplemented controls increasingly unacceptable. Long-term effects of adequate status may, therefore, only become apparent where food fortification has been initiated, and long-term health records kept. In Finland, VitD food fortification began in December 2002, and was doubled in 2010 as audit still showed inadequate VitD status, and deficiency since then has been virtually abolished, as above. Long-term population records for many of the chronic conditions discussed should prove of interest, especially since childhood T1DM rates have already fallen, as discussed. Disease rates should fall earliest in those disorders with the shortest development times, and prevalence rates for chronic disorders should begin to fall in subjects whose repletion started earliest in life, so that falls in chronic disease incidence may well be seen first in younger rather than in older people.

Much is expected of the large and very expensive VITAL trial giving Vitamin D and omega 3 FFAs to subjects vs. controls, which is due to complete this year [166]. This study has given fixed doses of Vitamin D3 of 2000IU/day and of omega 3 fatty acids in a four-arm RCT to subjects vs. controls in a multi-ethnic American population of ~20,000 men and women aged >50 and >55 years old respectively for 5 years. Baseline blood samples are planned in 16,000 and follow up samples on ~6000 of the subjects, and cancer and CVD risks are the primary outcomes. Hopefully the resultant data will allow stratification of the analyses by baseline, ± achieved, vitamin D status, in enough subjects for meaningful statistical analyses to be carried out using IPD, as well as by treatment group, in view of the obvious problems inherent to the latter type of analysis for nutrients. Furthermore, since testing outcomes for vitamin D supplementation dose given, rather than by VitD status, has now been shown to miss significant benefits for the correction of deficiency in increasing numbers of RCTs, as already discussed, makes this an important issue.

19.1. RCTs of VitD are confounded by many factors

RCTs of VitD are confounded by many factors common to all RCTs, including non-compliance, but for VitD they include non-assessment of baseline or achieved VitD status, personal supplement use, (whether or not 'allowed' in RCT protocols), variations in VitD intakes and in UVB exposure, and in intakes of other nutrients and from combining VitD with calcium which often increases non-compliance [164,167]. Additional problems are non-assessment of genetic factors, the use of RCT protocols used for drug trials (e.g. one dose 'fits-all'), in the expectation of comparable effects of supplementation in everyone in the treatment arm, when changes in status

actually vary widely with baseline status, and changes in patho-physiological response also vary with both baseline and achieved status, as well being confounded by non-adjustment for interacting nutrients, for genetic variants affecting the VitD axis, or for other environmental factors, as already discussed.

Another major problem in RCTs of VitD supplementation for chronic disorders is that pathological processes worsen over time, often beginning long before diagnosis, so that tissue damage is often well advanced at diagnosis. For example, atherosclerotic cardiovascular disease is progressive from childhood, the resultant fibrotic damage and loss of vascular reactivity increasing with age and increasingly unlikely to be reversible. However, the risk of acute events in chronic disease, e.g. following plaque disruption, or infective exacerbations in COPD, could be expected to be reduced by VitD repletion at any stage, likely contributing to the reductions in mortality, in CVD events and of acute infection rates in COPD already reported from re-evaluation of RCT data with the inclusion of vitamin D status, as already discussed.

Vitamin D has a wide range of biological effects [168], making RCTs looking at single outcomes inefficient; it would be rational, therefore, for future RCT design to ensure the inclusion of multiple health outcomes, over suitable time periods to increase trial cost-effectiveness both financially, and in subject and investigator manpower.

20. Expert commentary

The data presented and discussed in this review reports the high prevalence of vitamin D inadequacy globally and how this marks increases in health risks, including serious illness and early death, as is now being increasingly well documented. This is an easily avoidable problem and vitamin D3 is cheap to produce, especially in comparison with the savings likely from reductions in the numbers of patients needing treatment with costly medications and interventions that are suggested by the newer RCT data analyses reported here. Mechanistic evidence (using human as well as animal tissues) on the actions of activated hormonal vitamin D backs up the evidence of benefit suggested by clinical and epidemiological studies. With newer ways of analyzing RCT data, the use of stratification of subject data for baseline vitamin D status (using Individual Participant Data), and increasingly also for achieved status, definitive evidence of health benefits have already emerged for repletion of deficiency for many conditions, including CVD events and mortality, acute respiratory tract infections, asthma exacerbations, certain cancers and for T2DM]. While benefits of supplementation cannot be expected from short-term RCTs in chronic disorders that take many years to develop, like T2DM and cardiovascular diseases, records of population statistics before and after commencement of effective population-level supplementation (with proven avoidance of deficiency), may reveal that effective fortification leads to reductions in rates of such chronic disorders, over time.

Globally, the lack of positive action to ensure adequate overall vitamin D provision is becoming increasingly unacceptable. Governmental recommendations for individuals to ensure that they take enough vitamin D each day when their food provides so little, is rather like saying to a starving person, 'eat more', easy to do when food is plentiful and affordable, but impossible otherwise. Thus, although supplementation can correct deficiency, food fortification, as now provided very efficiently in Finland, would be a much more effective measure at the population-level, and would also be very cost-effective, especially where it is implemented voluntarily by food manufacturers.

21. Five year view

By 2023, I expect that public health records from Finland will be starting to show reductions in chronic disease rates since food fortification began there in 2006, and was doubled in 2010, virtually eliminating deficiency (as confirmed on audit). In particular, 15–20 years could be long enough for T2DM and CVD rates to have begun to fall (faster, that is, than the latter are already falling due to the improving management of both structural arterial disease and of acute events). I would also expect that many more countries will be providing food fortification and seeing reductions in acute illnesses such as infections.

Research on Vitamin D will be looking into details of as yet unsuspected roles of calcitriol, of other metabolites as they are discovered, and into disorders where mechanistic data suggests benefits but oral repletion has not produced them. In addition, newly recognized problems and as yet unknown effects of disease, such as the newly reported local tissue resistance to calcitriol in rheumatoid arthritis, will have been explained; hopefully they will also have been corrected, possibly by new analogues of calcitriol or of other recently discovered metabolites able to overcome such resistance. Solutions to disorders of the vitamin D axis, and its interactions, will be adding restoration of vitamin D function to the armory of measures available for the treatment of rheumatoid arthritis, and of those other conditions that may be found to have similar tissue resistance or as yet unrecognized disease-induced vitamin D dysfunction.

By 2023, no poorly designed RCTs of vitamin D supplementation will be in progress, or allowed to start, and many countries will be fortifying food with vitamin D and will have confirmed its efficacy in abolishing inadequacy. 25(OH)D assays will only be used in the management of medical conditions, for the audit of vitamin D status across population groups, for research into newly recognized disorders in the function of vitamin D, or for sorting out as yet unsuspected vitamin D dysfunction, whether due to interactions of this vitamin or of its many metabolites with other nutrients or due to other genetic or environmental factors.

Key issues

- As a vitamin, vitamin D is essential to life and for bone health, at all ages
- Vitamin D deficiency is common world-wide, both in tropical, temperate and other countries
- Foodstuffs provide too little vitamin D for adequate intakes to be achieved at the population level, world-wide, though people regularly eating a herring a day might escape deficiency

- Adequate exposure of skin to summer or tropical sunshine induces plentiful synthesis of vitamin D, but is increasingly rare due to covered up clothing (often worn by men and women) in both tropical, temperate and other countries, and to increasingly indoor patterns of both work and leisure
- Several thousand genes have vitamin D response elements in their promoter regions, explaining
- The proven modulation of function of many hundreds of genes by activated vitamin D, its multiple mechanistic and physiological effects on the body, and the reductions in risk of the increasing numbers of pathological conditions currently being identified from randomized controlled trial data when analyzed in initially deficient people
- Varying daily intakes of vitamin D are recommended across the globe, but they can rarely be met without the use of supplements and, since deficiency rates have remained high despite these recommendations for decades, they are clearly ineffective at the population level
- Food fortification with vitamin D is a cost-effective way to improve vitamin D repletion, and can abolish deficiency at the population level, removing the need for personal supplement usage, and this public health measure warrants world-wide implementation

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