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Diagnosis and treatment of vitamin D deficiency

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The recent discovery – in a randomised, controlled trial – that daily ingestion of 1100 IU of colecalciferol (vitamin D) over a 4-year period dramatically reduced the incidence of non-skin cancers makes it difficult to overstate the potential medical, social and economic implications of treating vitamin D deficiency. Not only are such deficiencies common, probably the rule, vitamin D deficiency stands implicated in a host of diseases other than cancer. The metabolic product of vitamin D is a potent, pleiotropic, repair and maintenance, secosteroid hormone that targets > 200 human genes in a wide variety of tissues, meaning it has as many mechanisms of action as genes it targets. A common misconception is that government agencies designed present intake recommendations to prevent or treat vitamin D deficiency. They did not. Instead, they are guidelines to prevent particular metabolic bone diseases. Official recommendations were never designed and are not effective in preventing or treating vitamin D deficiency and in no way limit the freedom of the physician – or responsibility – to do so. At this time, assessing serum 25-hydroxy-vitamin D is the only way to make the diagnosis and to assure that treatment is adequate and safe. The authors believe that treatment should be sufficient to maintain levels found in humans living naturally in a sun-rich environment, that is, > 40 ng/ml, year around. Three treatment modalities exist: sunlight, artificial ultraviolet B radiation or supplementation. All treatment modalities have their potential risks and benefits. Benefits of all treatment modalities outweigh potential risks and greatly outweigh the risk of no treatment. As a prolonged 'vitamin D winter', centred on the winter solstice, occurs at many temperate latitudes, ≤ 5000 IU (125 µg) of vitamin D/day may be required in obese, aged and/or dark-skinned patients to maintain adequate levels during the winter, a dose that makes many physicians uncomfortable.

Keywords: 25(OH)D, colecalciferol, ergocalciferol, treatment, vitamin D, vitamin D deficiency

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1. Introduction

Recently, Lappe *et al.* reported the first population-based, double-blind, randomised, placebo-controlled, interventional trial of colecalciferol (vitamin D) with non-skin cancer prevention as a principal secondary end point [1]. They found that 1100 IU of vitamin D and 1500 mg of calcium per day administered to 403 Nebraska women over 4 years dramatically reduced the relative risk (0.232) for incident cancers compared with 206 placebo controls ($p < 0.005$). Furthermore, baseline and treatment-induced serum 25-hydroxy-vitamin D (25[OH]D) levels were strong and independent predictors of cancer risk.

Besides cancer, vitamin D deficiency is associated with cardiovascular disease, hypertension, stroke, diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, periodontal disease, macular degeneration, mental illness, propensity to fall and chronic pain [2-6]. The recent meta-analysis

of 18 randomised controlled trials (RCTs) indicating that vitamin D, even in relatively low doses, reduces total mortality [7] adds to the growing evidence that this is a unique vitamin.

The vitamin D field is expanding so rapidly, and the diseases implicated so pervasive, that recent discoveries defy both the imagination and credulity. For example, a recent review presented considerable evidence that influenza epidemics, and perhaps other wintertime infections, are brought on by seasonal deficiencies in antimicrobial peptides secondary to seasonal deficiencies in vitamin D [8]. Recent post-hoc analysis of a RCT supported the theory, finding 2000 IU of vitamin D/day virtually eliminated self-reported incidences of colds and influenza [9].

Even the present twin childhood epidemics of autism [10] and type 1 diabetes [11], both of which occurred shortly after sun-avoidance advice became widespread, may be sequela of gestational or early childhood vitamin D deficiency. It is beyond the scope of this article to discuss all these diseases in detail, but the reviews cited above discuss many of them. Furthermore, such theories are just that, theories, and, like all theories, await further science. While we wait for the RCTs needed to clarify the role of vitamin D in the prevention of disease, a strong case already exists for diagnosing and treating vitamin D deficiency [12,13].

Other than its role in treating various bone diseases, we are only beginning to learn of the role vitamin D may have in treating disease. For example, a study of recurrence-free survival in early-stage, non-small-cell lung cancer patients found those with the highest vitamin D input had double the 5-year recurrence-free survival and better overall survival than those with the lowest [14]. This strongly implies a vitamin D treatment effect, that is, untreated vitamin D deficiency in non-small-cell lung cancer patients is a risk factor for early death. Because the anticancer mechanism of action of vitamin D (reducing cellular proliferation, inducing differentiation, inducing apoptosis and preventing angioneogenesis) is basic to all cancers, it is reasonable to hypothesise a general cancer treatment effect, at least in the early stages of cancer, when aberrant cells are more likely to retain the vitamin D receptor and the ability to activate vitamin D.

Furthermore, non-fatal, but life-impairing, conditions are also associated with vitamin D deficiency. For example, chronic idiopathic musculoskeletal pain, especially low back pain, is common in vitamin D deficient patients. In one study, 93% of patients with such pain had low 25(OH)D levels [15]. More recently, a cross-sectional population study of South Asian women found that chronic pain was three-times more common among those with the lowest 25(OH)D levels [16].

Several open studies have reported successful treatment of chronic pain with supplemental vitamin D [17,18]. In the largest study so far, 83% of 299 patients with idiopathic chronic low back pain were severely vitamin D deficient and the symptoms in the great majority of these patients dissipated after taking 5000 – 10,000 IU of 25(OH)D daily for 3 months [19]. A recent review pointed out the importance and effectiveness of diagnosing and treating vitamin D deficiencies in the rehabilitation setting [20], whereas a second study found high baseline 25(OH)D levels were associated with better functional status, shorter length of stay and better progress in rehabilitation [21].

The authors use cancer and chronic pain as examples for two reasons; the data linking these conditions to vitamin D deficiency are epidemiological and, until Lappe *et al.* [1], the studies showing a treatment or preventive effect were either epidemiological or open trials. This is true of virtually every disease associated with vitamin D deficiency other than metabolic bone disease, fractures and the risk of falls [22,23]. The lack of RCTs in the majority of diseases associated with vitamin D deficiency is an argument not to use vitamin D as adjuvant treatment for these conditions until such studies prove its effectiveness.

However, is that an argument not to diagnose and treat vitamin D deficiency? If human RCTs exist showing cigarette smoking is dangerous, the authors have yet to locate them. Instead, the compelling evidence for the dangerousness of smoking exists in convincing epidemiological data and the demonstration of a mechanism of action. The same is true for vitamin D, although the diseases linked to vitamin D deficiency outnumber those linked to cigarette smoking – as the above reviews indicate – and activated vitamin D, a secosteroid, has as many mechanisms of actions as genes it targets. Some would also argue that the quantity and quality of the epidemiological data for vitamin D is approaching that which existed for cigarette smoking when governments and medical bodies first acted.

2. Incidence of vitamin D deficiency

Adult vitamin D deficiency is endemic [24-26]. A high number of otherwise healthy children and adolescents are also vitamin D deficient [27,28]. Rickets, a disease of the industrial revolution, is resurgent in the US [29] and Great Britain [30]. Quite alarmingly – given mounting animal data that gestational vitamin D deficiency causes irreversible brain damage in offspring [31,32] – severe deficiencies are very common in newborn infants and pregnant women, especially African-Americans [33]. A population-based study of 2972 American women of childbearing age found 42% of African-American women in the US had 25(OH)D levels < 15 ng/ml and 12% had levels < 10 ng/ml [34]. Note that 25(OH)D levels are reported in the literature as either ng/ml or nmol/l (1 ng/ml equals 2.5 nmol/l).

Vitamin D deficiency is very common among in-patients, even at respected institutions. For example, a 1998 study of in-patients at Massachusetts General Hospital found 57% had 25(OH)D levels < 15 ng/ml [35]. A more recent study of Italian in-patients found that mean levels approached the

osteomalacic range [36]. Even in sunny Israel, a fourth of in-patients have such levels [37].

Furthermore, the definition of vitamin D deficiency is changing almost yearly as research shows the low end of ideal 25(OH)D ranges are much higher than we thought only a few years ago. Most of the aforementioned prevalence studies used outdated reference values for 25(OH)D and, therefore, greatly underestimate the incidence of vitamin D deficiency. Obviously, the higher the 25(OH)D cut-off point, the higher the percentage of the population with deficiency.

The critical question is, 'What is an ideal 25(OH)D level?' Levels needed to prevent rickets and osteomalacia (15 ng/ml) are lower than those that dramatically suppress parathyroid hormone levels (20 – 30 ng/ml) [38]. In turn, those levels are lower than levels needed to optimise intestinal calcium absorption (34 ng/ml) [39]. Neuromuscular performance in 4100 older patients steadily improved as 25(OH)D levels increased and peak performance was associated with levels ~ 38 ng/ml [40]. Lappe *et al.* [1] recently found that increasing mean baseline levels from 29 to 38 ng/ml was associated with a dramatic reduction in the incidence of internal cancers. Recent pooled meta-analyses estimated levels of 33 ng/ml were associated with a 50% lower risk of colon cancer [41] and levels of 52 ng/ml with a 50% reduction in the incidence of breast cancer [42].

Although some experts believe the lower limit of adequate 25(OH)D levels are in the low 30s [12,43], others recommend up to 40 ng/ml [44]; there is certainly no scientific consensus. Ideal levels are unknown, but are probably close to levels the human genome evolved on. Natural levels, that is, levels found in humans who live or work in the sun, are ~ 50 – 70 ng/ml – levels attained by only a small fraction of modern humans [45]. While we wait for scientific consensus, the question is, do we wait with 25(OH)D levels that reflect a sun-avoidant life style or is it safer to wait with levels normally achieved by humans living naturally in a sun-rich environment?

3. Vitamin D metabolism and physiology

Perhaps because the term vitamin D contains the word 'vitamin', most people wrongly assume it is like other vitamins, that is, they can obtain adequate amounts by eating a good diet. However, the natural diets most humans consume contain little vitamin D, unless those diets are rich in wild-caught, fatty fish. Small amounts of vitamin D are contained in fortified foods, such as fortified milk, orange juice and cereals in the US, and margarines in Europe, but such sources are usually minor contributors to vitamin D stores. Traditionally, the human vitamin D system began in the skin, not in the mouth.

The manufacture of vitamin D by skin is extraordinarily rapid and remarkably robust; production after only a few minutes of sunlight easily exceeds dietary sources by an order of magnitude [2]. Incidental sun exposure, not dietary intake, is the principal source of circulating vitamin D stores and to a degree that is a function of skin surface area exposed [46,47]. For example, when fair-skinned people sunbathe in the summer (one, full-body, minimal erythemal dose of ultraviolet B radiation [UVB]), they produce ~ 20,000 IU of vitamin D in < 30 min [48]. One would have to drink 200 glasses of American milk (100 IU/8-oz glass) or take 50 standard multivitamins (400 IU/tablet) in one sitting to obtain this amount orally.

Vitamin D normally enters the circulation after UVB from sunlight strikes 7-dehydro-cholesterol in the skin converting it through thermal energy to vitamin D3 or colecalciferol (vitamin D). When taken by mouth, the body metabolises vitamin D similarly to that generated in the skin. No matter how it arrives in the circulation, the liver readily hydroxylates vitamin D – using cytochrome P450 enzymes – to 25(OH)D, the circulating form of vitamin D. The serum half-life of 25(OH)D, as estimated from submariners deprived of sunlight, is ~ 60 days, although radioisotope tracer-based half-life estimates are considerably shorter.

The classic endocrine function of vitamin D begins when the kidney further hydroxylates 25(OH)D into $1,25(OH)_2D$, which then acts to maintain serum calcium through a series of direct effects on calcium absorption and excretion, and through a series of inter-relationships with serum phosphate and parathyroid hormone. Serum $1,25(OH)_2D$ levels are generally in the normal range or even high, when 25(OH)D levels are low, except in extreme vitamin D deficiency. Furthermore, endocrine $1,25(OH)_2D$ is an adaptive hormone (i.e., it is produced in response to calcium deficiency); $1,25(OH)_2D$ levels are typically low when calcium intake is high.

In the last 10 years, it has become clear that the vitamin D steroid hormone system includes more than this classic endocrine pathway used to preserve the calcium economy [49]. The cytochrome P450 enzyme that further hydroxylates 25(OH)D to $1,25(OH)_2D$ is present in a wide variety of human tissues other than kidney. That is, the hormone directly affects numerous cells and tissues via its autocrine, and presumed paracrine, functions [50]. Like all steroid hormones (hormone: from the Greek, to urge on), $1,25(OH)_2D$ acts as a molecular switch, activating > 200 target genes. Most organs in the body show evidence of end-organ responsiveness to $1,25(OH)_2D$ [51].

For example, the role of vitamin D on the expression of naturally-occurring human antibiotics, antimicrobial peptides (AMPs), has become evident only recently [52,53]. AMPs exhibit broad-spectrum antimicrobial activity against bacteria, fungi and viruses [54]. Both epithelial cells and macrophages increase expression of AMP on exposure to microbes, an expression that is dependent on the presence of vitamin D [55]. Pathogenic microbes stimulate the

production of a hydroxylase, which converts 25(OH)D to $1,25(OH)_2D$. This in turn, activates a suite of genes involved in defence.

In the macrophage, the presence of vitamin D also appears to suppress the pro-inflammatory cytokines, IFN-γ, TNF-α and IL-12 [55]. Thus, vitamin D appears to both enhance the capacity of the innate immune system to produce endogenous antibiotics and – at the same time – dampen certain arms of the adaptive immune response, especially those responsible for the signs and symptoms of acute inflammation.

Plasma levels of vitamin 25(OH)D in African-Americans, known to be much lower than white-skinned individuals, are inadequate to fully stimulate the vitamin D-dependent antimicrobial circuits within the innate immune system [56]. However, the addition of 25(OH)D restored the dependent circuits and enhanced expression of the AMP, cathelicidin. As discussed below, high concentrations of melanin in the skin slows the production of vitamin D and ageing greatly reduces skin production. Therefore, easily-correctable deficiencies in innate immunity probably exist in many people, particularly dark-skinned and aged individuals, especially in the winter.

Most importantly, and unlike any other steroid hormone, substrate concentrations are absolutely rate-limiting for $1,25(OH)_2D$ production. The enzyme that first hydroxylates vitamin D in the liver and the enzyme in tissue that subsequently hydroxylates 25(OH)D to form $1,25(OH)_2D$, both operate below their respective Michaelis-Menten constants throughout the full range of their normal substrate concentrations (i.e., the reactions follow first-order mass action kinetics) [57]. Tissue levels of $1,25(OH)_2D$ directly depend on 25(OH)D blood levels, which, in turn, directly depend on the amount of vitamin D made in the skin or put in the mouth.

That is, the rate-limiting step for the production of this secosteroid is unique; tissue concentrations of $1,25(OH)_2D$ are directly dependent on 25(OH)D levels and 25(OH)D levels are entirely dependent on human behaviour. Therefore, the step into the sun, into the shade, to the supplements or to the sunscreen, rate-limits tissue $1,25(OH)_2D$ levels. Such extraordinary rate limitations are not only unique for a steroid hormone, they are key to understanding the remarkable pharmacology of vitamin D.

4. Factors affecting vitamin D levels

Factors that affect cutaneous production of vitamin D include latitude, season, time of day, air pollution, cloud cover, melanin content of the skin, use of sunblock, age and the extent of clothing covering the body. When the sun is low on the horizon, atmospheric ozone, clouds and particulate air pollution deflect UVB radiation away from the surface of the Earth. Therefore, cutaneous vitamin D production is effectively absent early and late in the day and for the entire day during several wintertime months at latitudes > 35°.

For that reason, vitamin D deficiency is more common the further poleward the population. For example, Boston, Massachusetts (latitude 42°) has a 4-month 'vitamin D winter' centred around the winter solstice when no UVB penetrates the atmosphere and an even longer period in the fall and late winter when UVB only penetrates around solar noon. In northern Europe or Canada, the 'vitamin D winter' can extend for 6 months. Furthermore, properly applied sunblock, common window glass in homes or cars, and clothing, all effectively block UVB radiation – even in the summer. Those who avoid sunlight – at any latitude – are at risk any time of the year. For example, a surprisingly high incidence of vitamin D deficiency exists in Miami, Florida despite its sunny weather and subtropical latitude [58].

African-Americans, the elderly and the obese face added risk. As melanin in the skin acts as an effective and ever-present sunscreen, dark-skinned patients need much longer UVB exposure times to generate the same 25(OH)D stores compared with fair-skinned patients [59]. The elderly make much less vitamin D than 20-year-olds after exposure to the same amount of sunlight [60]. Obesity is also major risk factor for vitamin D deficiency with obese African-Americans at an even higher risk [61]. Therefore, those who work indoors, live at higher latitudes, wear extensive clothing, regularly use sunblock, are dark-skinned, obese, aged or consciously avoid the sun, are at high-risk for vitamin D deficiency.

5. Diagnosis of vitamin D deficiency

Metabolic bone disease, prevention of falls and fractures, and treatment of secondary hypothyoidism are the classic reasons to treat with vitamin D. Nevertheless, the treatment of asymptomatic vitamin D deficiency is the most common reason to prescribe vitamin D. However, like all diagnoses, one must think of it before one can make it. Then, like any diagnosis, the physician must confirm it or rule it out by means of history, physical examination and laboratory assessment.

The classic presentation of severe vitamin D deficiency is metabolic bone disease in adults and rickets – with or without hypocalcaemic tetany – in children, a subject recently reviewed by Holick [2]. Osteomalacia (unmineralised collagen matrix) presents after the epiphyseal plates fuse and can occur in adolescence. Stress fractures – in otherwise healthy adolescents and adults – may indicate vitamin D deficiency [62]. Unexplained fractures in childhood may be rickets and not child physical abuse [63-65]. Radiographs of the wrist, alkaline phosphatase, and 25(OH)D level must be obtained before making life-altering – and false – accusations.

Vitamin D deficiency often presents with common, non-specific symtoms, such as muscular weakness – predominantly of the proximal limb muscles – a feeling of heaviness in the legs, chronic musculoskeletal pain,

fatigue or easy tiring [66]. The pain may have a hyperaesthetic quality. Osteomalacia may masquerade as fibromyalgia [67]. Physical examination is usually unremarkable, but may reveal undue pain on sternal or tibial pressure. However, the vast majority of cases are asymptomatic.

The aged may be wheelchair-bound secondary to vitamin D-deficiency-induced myopathy, yet they typically recover their mobility after treatment [68]. The recent strong association of low mood and cognitive impairment in the aged with vitamin D deficiency [69] suggests that such presentations may occur in the aged. A blinded, interventional trial found 4000 IU of vitamin D/day improved the mood of endocrinology out-patients [70], but there are no interventional studies of its effects on cognition.

Even without physical signs or symptoms, the physician should screen those at risk. Obtaining and properly interpreting a serum 25(OH)D level is the only way to make the diagnosis and should be assessed at least twice yearly in any patient at risk, once in the early spring for the nadir and once in the late summer for a peak level [71].

It warrants repeating, that serum $1,25(OH)_2D$ levels play no role in diagnosing the condition. The kidney tightly controls serum $1,25(OH)_2D$ levels, which are often normal or even elevated in vitamin D deficiency. Therefore, a patient with normal or high $1,25(OH)_2D$ serum levels, but low 25(OH)D levels, is vitamin D deficient despite high serum levels of the active hormone.

How can it be that a patient with normal or even high circulating levels of the active form of vitamin D is somehow vitamin D deficient? The most straightforward answer is that the endocrine and autocrine functions of vitamin D are quite different. However, that is too simple an explanation as serum $1,25(OH)_2D$ is plainly delivered to the cells via the systemic circulation. A few points may help resolve the apparent paradox.

First, patients with osteomalacia absorb calcium very poorly, despite their usually normal serum level of $1,25(OH)_2D$. For unclear reasons, 25(OH)D must also be present in the serum if the intestinal mucosal response to $1,25(OH)_2D$ is to occur. Second, in many of the animal models or cell culture systems the concentration of $1,25(OH)_2D$ needed to produce a particular effect is higher than can be achieved at physiological serum concentrations of $1,25(OH)_2D$. Apparently, the required higher concentration of $1,25(OH)_2D$ must be produced intracellularly, in an autocrine manner, using circulating 25(OH)D as the substrate.

For example, this appears to be the case with human myelodysplasia and with psoriasis, both of which respond to high systemic doses of $1,25(OH)_2D$ (but at a potential cost of hypercalcaemia). In some of the tumour model systems, and possibly in human myelodysplasia and psoriasis, the afflicted cells appear to have lost the ability to synthesize their own $1,25(OH)_2D$, a mutation that may be important in the pathogenesis of the disorder. Whatever the ultimate explanation, there is consensus that serum $1,25(OH)_2D$ is only a measure of the endocrine function of vitamin D and not an indicator of body stores or the ability of vitamin D to perform its pleiotropic autocrine functions.

6. Treatment of vitamin D deficiency

Three options exist for the treatment of vitamin D deficiency: sunlight, artificial UVB light or supplements; all have drawbacks. A total of 15 min of summer noonday sun or artificial UVB radiation (such as tanning beds) on both sides of the bare body will input ~ 10,000 IU of vitamin D into the systemic circulation of most light-skinned adults. One or two such exposures a week should maintain 25(OH)D levels in healthy ranges. Those who chose UVB light for vitamin D repletion, from either sunlight or artificial sources, should avoid sunburns, which are associated with malignant melanoma. Furthermore, they should understand that regular ultraviolet (UV) exposure ages the skin and increases the risk of non-melanoma skin cancers.

The treatment of choice for human vitamin D deficiency is human vitamin D, colecalciferol, also known as vitamin D_3. Oral vitamin D treatment is more difficult than treatment with UVB light for several reasons. First, unexpectedly high doses of vitamin D may be needed to achieve adequate serum 25(OH)D levels (1000 IU of vitamin D sounds like a lot; in fact, it is only 25 µg; that is, 1 µg is 40 IU). Second, the amount of vitamin D needed varies with body weight, body fat, age, skin colour, season, latitude and sunning habits. Third, unlike sun exposure, toxicity is possible with oral supplementation – although it is extraordinarily rare.

Colecalciferol is available over the counter in the US (but not in England) and via the internet in 400-, 1000-, 2000- and (recently) 5000-, 10,000- and 50,000-IU capsules. Colecalciferol 1000 IU/day will usually result in about a 10-ng/ml elevation of serum 25(OH)D when given over 3 – 4 months. Therefore, a patient with an initial level of 10 ng/ml would generally require 3000 IU/day for several months to achieve a level of 40 ng/ml and 4000 IU/day to achieve a level of 50 ng/ml – in the absence of cutaneous UVB exposure. However, its kinetics are not linear, 1000 IU/day will substantially raise low baseline levels, but a similar dose will not increase higher baseline levels by a similar increment. Treatment of vitamin D deficiency with $1,25(OH_2)D$ (calcitriol) or analogues of $1,25(OH_2)D$ (paricalcitol, doxercalciferol) are inappropriate, ineffective, dangerous and contraindicated.

The only prescription vitamin D preparation available in the US and England is the vitamin D analogue, ergocalciferol (vitamin D_2), available as 50,000-IU (1.25-mg) capsules. Physicians can easily replete most vitamin D deficient patients by giving one or two 50,000-IU doses of ergocalciferol weekly for 8 – 16 weeks and then maintain 25(OH)D levels > 40 ng/ml with 50,000-IU doses every 1, 2 or 4 weeks. The frequency of dosing depends on pre-existing 25(OH)D levels, age, skin colour, obesity, season, body weight and sun

avoidance. However, ergocalciferol is not human vitamin D, it may be a weaker agonist, it is not normally present in humans and its consumption results in metabolic by-products not normally found in humans [72]. It is also two- to four-times less effective than colecalciferol in raising 25(OH)D levels [73,74].

Recently, 50,000-IU capsules of colecalciferol (vitamin D_3) became available at some health-food stores in the US and over the internet. Grey *et al.* recently treated 21 vitamin D-deficient patients with 50,000 IU of colecalciferol weekly for 4 weeks, then 50,000 IU monthly for 1 year [75]. Blood levels rose from a mean of 11 ng/ml at baseline to 30 ng/ml at 6 months and to 31 ng/ml at 1 year, indicating such doses do not achieve natural 25(OH)D levels and that 25(OH)D levels do not continue to rise after 6 months of such treatment.

Cod liver oil contains a variable amount of vitamin D, but usually contains high amounts of vitamin A. Consumption of preformed retinols, even in amounts consumed by many Americans, may be causing low-grade, but widespread, bone toxicity [76]. Vitamin A antagonises the action of vitamin D [77] and high retinol intake thwarts the protective effect of vitamin D on distal colorectal adenoma [78]. Different brands of cod liver oil contain variable amounts of vitamin D, but usually high amounts of vitamin A; the authors do not recommend cod liver oil.

It is important to understand that neither the regular consumption of recommended amounts of vitamin D (e.g., 400 IU of vitamin D in a multivitamin) nor the regular consumption of vitamin D fortified foods (e.g., 100 IU/8-oz glass of milk) effectively prevents vitamin D deficiency [79,80]. Furthermore, 2000 IU/day for 1 year failed to achieve a 32 ng/ml target 25(OH)D concentration in 40% of 104 African-American women studied [81]. Even the administration of 4000 IU/day for > 6 months to middle-age Canadian endocrinology out-patients, resulted in average 25(OH)D levels of 44 ng/ml and produced no side effects other than an improved mood [70]. Heaney estimated that ~ 3000 IU/day of vitamin D is required to assure that 97% of Americans obtain levels > 35 ng/ml [43]. Healthy adult men use between 3000 and 5000 IU of vitamin D/day, if it is available [82].

In general, the more the patient weighs, the more vitamin D will be required and large amounts of body fat further increases requirements. Not only are baseline 25(OH)D levels lower in the obese, they require higher doses of either oral supplements or UV irradiation than lean individuals in order to obtain the same increases in 25(OH)D blood levels [83]. Fat malabsorption syndromes may increase requirements or necessitate the use of UV radiation. Advancing age impairs the ability of the skin to make vitamin D, so older people often need higher doses than younger people. Therefore, dark-skinned, large, obese and older patients often require higher maintenance doses than fair-skinned, small, thin or younger patients. Loading doses of colecalciferol 10,000 IU/day for several weeks are safe to use before beginning maintenance therapy.

Physicians who do not want their patients exposed to UV radiation and who do not monitor 25(OH)D levels should recommend daily supplementation with colecalciferol 2000 IU for their adult and adolescent patients, and properly document their recommendations. However, they should know that such doses will not always achieve natural levels – especially in the winter – in the most vulnerable segments of the population. The authors recommend that bottle-fed infants be supplemented with 400 IU of vitamin D daily and breast-fed infants with 800 IU daily. Older infants and toddlers may be at extremely high risk during weaning, after they stop fortified infant formula and begin consuming unfortified juices. Toddlers and older children, who do not go into the sun, should take 1000 – 2000 IU/day, depending on body weight.

Vitamin D deficiency in pregnancy is an on-going epidemic [84] and animal evidence continues to accumulate that maternal vitamin D deficiency permanently injures foetal brains [31,32,85]. Pregnant women – or women thinking of becoming pregnant – should have 25(OH)D levels checked every 3 months, be adequately treated as outlined above and the advice should be documented in their medical records [86]. For those who wonder how vitamin D could be important for brain development, given its historically low levels in most breast milk, Hollis and Wagner discovered that breast milk is always a rich source of vitamin D – enough to maintain natural levels in infants – as long as lactating mothers take 6,000 IU of vitamin D daily [87].

Cytochrome P450 enzymes are responsible for both the initial metabolism and subsequent catabolism of vitamin D. Therefore, drugs dependent on cytochrome P450 enzymes – and there are many – may effect vitamin D metabolism. What clinically relevant interactions cytochrome P450 metabolised substances – including cardiac drugs, erythromycins, psychotropics and even grapefruit juice – have on the metabolism of vitamin D is an area awaiting further research. Patients on such drugs should have frequent 25(OH)D level checks when being treated for vitamin D deficiency.

Of the research done on drug/vitamin D interactions, anticonvulsants [88], corticosteroids, cimetidine, antituberculosis agents, theophylline and orlistat may lower 25(OH)D levels, whereas thiazide diuretics increase 25(OH)D levels [89]. Furthermore, a number of studies found estrogen and progesterone raised $1,25(OH)_2D$ levels, whereas the literature suggests testosterone is unlikely to be a major factor in vitamin D metabolism [89]. This raises the possibility that some of the increased longevity of women compared with men is due to sex-discrepant metabolism of vitamin D. The recent discovery that atorvastatin significantly increases 25(OH)D levels suggests that some – or all – of the anti-inflammatory effects of statins may be mediated through increases in vitamin D levels [90].

7. Vitamin D toxicity

Vitamin D toxicity (usually asymptomatic hypercalcaemia) is exceedingly rare and few practicing physicians have ever seen a case [91], although that could change with the recent over-the-counter availability of 50,000-IU capsules. True toxicity is secondary to the unbridled effects of hypercalcaemia. First urine calcium, and then serum calcium, will begin to gradually increase when 25(OH)D levels exceed some level > 150 ng/ml and such levels must be associated with hypercalcaemia in order to indict vitamin D [2,48]. True toxicity results when hypercalcaemia goes undetected and calcifies internal organs, especially the kidneys. In order to produce hypercalcaemia, most adults would have to take well in excess of 10,000 IU/day for many months or even years. Most patients with vitamin D toxicity recover fully by simply stopping the vitamin D and practicing strict sun-avoidance.

Despite robust skin production, vitamin D toxicity cannot occur from skin production. Once maximum cutaneous production occurs, additional sun exposure will not result in additional net input to the system. The same UVB that produces vitamin D in the skin also degrades it, causing a steady-state that generally limits cutaneous production to a maximum of ~ 20,000 IU/day. For this reason, in spite of such robust cutaneous production, no one has ever reported vitamin D toxicity from either sun exposure or from exposure to artificial UVB light.

Credible evidence of vitamin D toxicity in adults chronically consuming ≤ 10,000 IU of supplemental colecalciferol a day is absent in the literature. In fact, other than pharmaceutical manufacturing errors, the literature contains few cases of colecalciferol toxicity from supplement use; virtually all the reported cases of hypercalcaemia are from faulty industrial production, labelling errors, dosing errors and in patients treated medically with high doses of ergocalciferol.

The present upper limit for medically unsupervised intake by adults and children over the age of 1, set by the Institute of Medicine's Food and Nutrition Board in 1997, is 2000 IU/day, a limit that is based on old – and many feel – faulty, literature [92]. Although a 2000 IU upper limit may be appropriate for young children, such limits in older children, adolescents and adults have the effect of both limiting effective treatment of vitamin D deficiency and impairing dose-appropriate interventional research. However, the present 2000 IU/day upper limit no more impairs the ability of physicians to treat vitamin D deficiency with higher doses than comparable upper limits for calcium or magnesium impair the ability of physicians to treat those deficiencies with doses above the upper limit, once properly diagnosed.

That said, physicians who use higher doses may feel more comfortable periodically monitoring 25(OH)D levels. Periodic 25(OH)D levels will also educate the physician, not only to the safety of supplementation, but to the surprisingly high oral dose required to achieve and then maintain adequate serum 25(OH)D levels, especially in the fall and winter.

8. Absolute and relative contraindications to treatment

The only absolute contraindication to vitamin D supplementation is vitamin D toxicity or allergy to vitamin D, although – to the best of the authors' knowledge – there are no reports in the literature of acute allergic reactions to vitamin D supplements. Contraindications to sunlight or artificial UV radiation include a number of dermatological conditions (porphyrias, xeroderma pigmentosum, albinism), as well as various photosensitisers (sulfonamides, phenothiazines, tetracyclines, psoralens). Previous skin cancers, especially cutaneous melanoma, are contraindications to excessive UV exposure, although a recent study found reduced mortality in melanoma patients who had continued exposure to sunlight [93]. However, for a number of reasons – including medical-legal reasons – the authors recommend oral treatment for patients who have had any type of skin cancer.

Although the liver initially metabolises vitamin D, liver disease is not a contraindication to treatment of deficiency. The liver conserves the ability to hydroxylate vitamin D despite advanced liver disease [94]. In fact, a recent study of patients with advanced non-cholestatic chronic liver disease recommended treatment of concomitant vitamin D deficiency after finding that serum 25(OH)D levels of < 10 ng/ml predicted coagulopathy, hyperbilirubinaemia, hypoalbuminaemia, anaemia and thrombocytopaenia [95].

Vitamin D hypersensitivity syndromes – often confused with vitamin D toxicity – occur when extrarenal tissues produce $1,25(OH)_2D$ in an unregulated manner causing hypercalcaemia [96]. They are diagnosed by measuring serum calcium (elevated), 25(OH)D (normal or low) and $1,25(OH)_2D$ (elevated) levels. Vitamin D hypersensitivity syndromes can occur in some of the granulomatous diseases (especially sarcoidosis and tuberculosis) and cancer (especially lymphoma). Such syndromes are a relative contraindication to treatment. Indeed, in the past, routine treatment of such syndromes consisted of iatrogenic production of deficiency by restriction of oral vitamin D and avoidance of sunlight.

Recently, some have questioned the wisdom of withholding vitamin D in vitamin D deficient hypercalcaemic patients. For example, not only is vitamin D deficiency a contributing factor to metabolic bone disease in primary hyperparathyroidism (PHPT), some patients diagnosed with PHPT may actually have the disease secondary to vitamin D deficiency [97]. Furthermore, recent data indicate that high-dose vitamin D repletion in 21 hypercalcaemic PHPT patients did not exacerbate hypercalcaemia

and reduced abnormalities in calcium, phosphate and parathyroid hormone. [75].

Similar questions arise about withholding vitamin D in hypercalcaemic tuberculosis patients, as many tuberculosis patients – especially dark-skinned patients – are likely to be severely vitamin D deficient [98]. A recent controlled study indicated adjuvant vitamin D 10,000 IU/day improved sputum conversion rates compared with conventional treatment alone [99]. An earlier study showed adjuvant vitamin D helped treatment and – surprisingly – children with tuberculosis given adjuvant vitamin D were less likely to be hypercalcaemic than children given only standard treatment [100]. An antimicrobial treatment effect is consistent with recent research, mentioned above, indicating vitamin D upregulates naturally-occurring – and broad spectrum – antimicrobial peptides.

Therefore, hypercalcaemia is a relative contraindication to vitamin D, sunlight or artificial UVB radiation. The physician should carefully evaluate any hypercalcaemic patient for the cause of their hypercalcaemia. Once the cause of the hypercalcaemia is clear, if the physician decides to treat concomitant vitamin D deficiency – despite the hypercalcaemia – they should only do so if the hypercalcaemia is mild-to-moderate (< 12 mg/100 ml) and proceed cautiously, frequently monitoring urine and serum calcium, 25(OH)D, and $1,25(OH)_2D$ levels.

9. Summary

Vitamin D deficiency is endemic and associated with numerous serious diseases. Understanding the physiology of vitamin D and having a high index of suspicion are keys to suspecting the diagnosis. Serum 25(OH)D levels < 40 ng/ml are seldom found in humans living naturally in a sun-rich environment. Treatment with sunlight or artificial UVB radiation is simple, but increases the risk of non-melanoma skin cancers and ages the skin. Sunburns increase the risk of malignant melanoma. Adequate oral supplementation will require doses that make many physicians uncomfortable.

10. Expert opinion

Perhaps a new era is on medicine, the vitamin D era; although – given past false claims for medical benefits of vitamins – others may suspect instead a vitamin D error. That said it is difficult to think of a common disease that has not been associated with vitamin D deficiency in a high-quality epidemiological study. The difference between vitamin D and other vitamins is that this remarkable prehormone is the only known substrate for a 'repair and maintenance' secosteroid hormone, whose mechanisms of action are limited only by the number of genes it regulates and whose local tissue concentrations are rate-limited by human behaviour.

Although the existence, depth and breadth of any vitamin D era remains to be seen, a burgeoning literature points to horizons beyond our vision and questions that sound sophomoric to ask. For example, are the diseases of civilisation mainly the diseases of vitamin D deficiency? Are influenza and other viral respiratory diseases symptoms of vitamin D deficiency, in the same manner that *Pneumocystis carinii* pneumonia is a symptom of AIDS [8]? Do African-Americans die prematurely simply because they have 25(OH)D levels about half that of white patients [101]? The Centers for Disease Control and others have repeatedly found that neurodevelopment disorders such as mild mental retardation are more common in African-Americans than white patients [102,103] even after control for socioeconomic factors [104]. Is this simply because African-American fetuses are more likely to develop in vitamin D deficient wombs? Is the present dramatic increase in the prevalence of autism over the last 20 years simply the result of medical advice to avoid the sun over that same 20 years [10]?

If only a fraction of the answers to these questions is yes, what will be the result for medicine, society, government and the medical industry? For example, instead of a 60% reduction in incident cancers that Lappe *et al.* [1] found, say vitamin D only provides a 30% reduction? What effect would such a reduction have on government health programs, pensions, oncologists, clinics, hospitals and anticancer drug manufacturers? Furthermore, given the relatively small dose of vitamin D Lappe *et al.* [1] used, is it reasonable to hypothesise that higher daily doses would have prevented > 60% of incident cancers?

Before we herald a vitamin D era, epidemiological evidence must give way to larger RCTs, both in prevention and treatment. Such studies should use human vitamin D (colecalciferol), given daily, in doses adequate to ensure a treatment effect is not missed (2000 – 10,000 IU/day), with periodic monitoring of 25(OH)D levels both to ensure treatment compliance and to confirm that natural 25(OH)D levels (50 – 70 ng/ml) are obtained by the interventional arm.

However, given what we know today, present government recommendations for 'adequate intake' are clearly inadequate and need upward revision. Just as important, present 'upper limits' do not reflect the modern toxicology literature. In fact, many adult patients – if not most – will need to exceed the upper limit simply to maintain natural serum levels.

Likewise, present food fortification strategies are inadequate and leave the most vulnerable members of our society with levels that endanger their health. Both the amount used and the number of foods fortified need upward revision. Mandatory fortification of juices, not just infant formula, would help fortify toddlers during and after weaning, and mandatory fortification of cereal grain products and cheeses would ensure a supply to African-Americans, many of whom do not drink milk.

To the authors' knowledge, plaintiffs' attorneys are not yet involved in the vitamin D debate. After the findings of Lappe *et al.* [1], it may only be a matter of time until lawsuits against physicians begin to appear, claiming that

physicians dispensed sun-avoidance advice, but negligently failed to diagnose and treat the consequent vitamin D deficiency, leading to fatal cancers. Unless the future literature fails to support the present, such medical malpractice suits may become commonplace.

Finally, physicians and policy-makers should understand that much of the future of vitamin D is out of their hands. Inexpensive high-dose vitamin D supplements are now widely available to the American public over-the-counter and to the world via the internet. Sunlight remains free. A Google search for 'vitamin D' reveals several million hits. After the Canadian Cancer Society recently recommended 1000 IU/day for all Canadian adults in the wintertime, vitamin D disappeared off the shelves, causing a shortage during the summer.

The pleiotropic actions and unique pharmacology of vitamin D mean educated patients, on their own, can entirely control their own tissue levels of this steroid, through either UVB exposure or over-the-counter supplementation. Given the attitudes that some in mainstream medicine have about any substance with the word 'vitamin' in it [105], the public and not the medical profession may be the first to enter the vitamin D era.

Declaration of interest

J Cannell heads the non-profit educational organisation, the Vitamin D Council. B Hollis is a consultant to the DiaSorin Corporation.

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