Handbook of vitamin D in human health

Prevention, treatment and toxicity

edited by:
Ronald Ross Watson

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Table of contents

Overview of key vitamin D modified conditions

1. Vitamin D deficiency in the 21st century: an overview 13
S.S. Oberhelman and T.D. Thacher

2. Vitamin D in health of seniors 39
F. Lauretani, M. Maggio, C. Ruggiero, G.P. Ceda and L. Ferrucci

3. Vitamin D supplementation and public health policy 53
R. Babaria and R.R. Watson

Vitamin D and musculoskeletal health

4. Vitamin D and fall risk 67
J. Basran, R.L. Duckham and D.B. Hogan

5. The beneficial effects of higher (adequate) vitamin D status on bone growth and muscle strength in children and adolescents 83
L.H. Foo and S.J. Whiting

6. Hypovitaminosis D and muscle strength 97
T. Songpatanasilp

7. Vitamin D and growth 115
H.T. Viljakainen and E. Hyppönen

8. Vitamin D and arthritis 137
U.J. Haque

9. High-dose vitamin D supplementation in the elderly 147
C.J. Bacon

Vitamin D and chronic disease

10. Vitamin D deficiency and premature death 175
A. Zittermann and S. Prokop

11. Vitamin D and hyperparathyroidism in patients with chronic kidney disease 193
D. Hansen

12. Diseases affected by vitamin D: sun exposure 207
W.B. Grant

13. Immune modulation by UV: role of vitamin D 227
P.H. Hart and S. Gorman

14. Vitamin D and periodontal disease 243
N. Garcia, D. Miley and D.A. Dixon

15. Vitamin D and cystic fibrosis 255
T. Pincikova and M. Flodström-Tullberg

Vitamin D and infectious disease

16. Vitamin D and respiratory infections in infants and toddlers: a *nutri-shine* perspective 277
K.V. Balan, U.S. Babu, D.E. Godar and M.S. Calvo

17. Vitamin D in HIV/AIDS: a role? 299
J.-P. Viard and J.-C. Souberbielle

18. Vitamin D and tuberculosis 321
K. vinh quốc Lương and L.T.H. Nguyễn

19. Vitamin D and dental health 355
E. Jordan, S. Davis, P. Rakes, L.K. McCauley and J. Bashutski

20. Inflammation and vitamin D 373
X. Guillot, C. Prati, N. Saidenberg-Kermanac'h, L. Semerano, G. Falgarone, M.C. Boissier and D. Wendling

Vitamin D and cancer

21. Vitamin D in the prevention and treatment of pancreatic cancer 393
T.C. Chen and K.C. Chiang

22. Vitamin D and melanoma 419
J.A. Newton-Bishop and J.A. Randerson-Moor

23. Vitamin D autocrine system and prostate cancer prevention and treatment 445
T.C. Chen

24. Vitamin D and esophageal cancer 465
H.G. Coleman, M.M. Cantwell and L.J. Murray

25. Monitoring *in vivo* immune modulation by vitamin D in multiple sclerosis 475
A.-H. Muris, J. Damoiseaux and J. Smolders

Vitamin D in chronic diseases

26. Vitamin D and insulin sensitivity 503
B. Larrick, S. Donkin and D. Teegarden

27. Vitamin D and diabetes mellitus: where are we? 527
J. Liu

28. Vitamin D and cardiovascular risk: hype or new hope? 549
J.L. Anderson and J.B. Muhlestein

29. Vitamin D and transplantation 567
M. Courbebaisse, J.C. Souberbielle and E. Thervet

30. Vitamin D and bone health among people with epilepsy 589
R.A. Shellhaas, R.K. Singh and S.M. Joshi

Women and children

31. Neonatal effects of enhanced vitamin D and vitamin D for premature infants 609
H.K. Linke

32. Lactation and vitamin D 633
S.N. Taylor, C.L. Wagner and B.W. Hollis

33. Vitamin D replacement in pregnant women in developing countries 651
M.T. Sahu and M. Sahu

34. Vitamin D in pregnancy 671
D. Dror

35. Design and rationale of the *VI*Tamin D and Omeg*A*-3 Tria*L* (VITAL) 693
S.S. Bassuk and J.E. Manson

Index

About the edtior 729

Overview of key vitamin D modified conditions

Key facts

- Historically, vitamin D deficiency was defined by the clinical disease of rickets, which was nearly eradicated through vitamin D fortification.
- Presently, defining optimal vitamin D status based on concentrations of the serum 25-hydroxyvitamin D (25(OH)D) metabolite is controversial. The functional consequences of a given 25(OH)D concentration are highly variable within the population, but up to one billion people worldwide may have less than optimal vitamin D status.
- Vitamin D is actually a hormone, not a true vitamin. It can be ingested (naturally occurring in fatty fish, fortified in some foods such as milk or in supplement form) or dermally synthesized with exposure to ultraviolet light.
- Observational studies have demonstrated relationships between vitamin D status and infectious, immune, metabolic, degenerative, and neoplastic diseases, but the beneficial effect of vitamin D in these conditions requires confirmation with randomized controlled trials.
- Identifying markers of the diverse functional effects of vitamin D will permit an individualized approach to vitamin D supplementation, based on health risks.

Summary points

- Vitamin D deficiency causes the clinical disease of nutritional rickets, which causes softening and bending of the bones.
- The incidence of vitamin D-deficiency rickets declined dramatically with fortification of milk and foods with vitamin D.
- A recent worldwide resurgence of rickets has been recognized, possibly related to reduced intake of vitamin D, breastfeeding practices, increasing prevalence of obesity, sun avoidance and sunscreen use, and air pollution.
- Vitamin D status is currently defined by the serum 25(OH)D concentration, which is a marker of storage rather than function. Laboratory assays for measurement of 25(OH)D vary widely.
- There is no universally accepted serum-based definition of vitamin D deficiency, but nutritional rickets occurs at very low 25(OH)D concentrations.
- The Institute of Medicine recommended 600 IU of vitamin D daily for most adults. However, several intermittent dosing regimens have been proposed for skeletal and non-skeletal health benefits.
- The health benefits of sufficient vitamin D may extend far beyond bone health. Observational studies suggest that vitamin D may benefit immunity, cardiovascular health, several cancers, pain, and muscle strength.
- Wide variation in individual responses to vitamin D exists. As personalized medicine becomes more of a reality, and the non-skeletal benefits of vitamin D are better defined, recommended vitamin D intake will need to be personalized.

1. Vitamin D deficiency in the 21st century: an overview

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Abstract

Vitamin D deficiency in the past was defined by the clinical recognition of nutritional rickets, a disease nearly eradicated by vitamin D fortification. Today, the definition of vitamin D deficiency is controversial, and is based on serum concentrations of 25-hydroxyvitamin D (25(OH)D), a marker of storage rather than of function. The level of 25(OH)D that is optimal for bone health may differ from that required for non-skeletal benefits. Observational studies suggest wide-ranging effects of vitamin D status on metabolic, immunologic, infectious, cardiovascular, neoplastic, and degenerative disorders. There is likely wide individual variation in the functional implications of a given level of 25(OH)D. As randomized controlled trials confirm the benefits of vitamin D in non-skeletal diseases, the recommended intake of vitamin D and optimal 25(OH)D concentration may need to be adjusted to account for these outcomes. The future will bring an individualized approach to assessing vitamin D status and needs. Even when the factors known to influence 25(OH)D concentrations are accounted for, most of the individual variation of 25(OH)D values is difficult to explain. This variation is partially explained by genotypic variants of the vitamin D binding protein, vitamin D receptor, and the hydroxylase enzymes of the vitamin D metabolic pathway. With more widespread use of genome-wide analysis, it may be possible to personalize an individual's vitamin D requirement, particularly in view of other disease risk factors. Measurement of the physiological effects of vitamin D that relate to bone metabolism, the immune system, or other effectors of disease could allow tailoring of the dose of vitamin D to attain maximal physiological benefit. Additional markers of the functional response to vitamin D at the individual level may be available in the future. Vitamin D has exciting potential, and a flurry of research activity is now underway to explore its potential benefits.

Keywords: rickets, hypovitaminosis D, public health, deficiency, personalized medicine

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Abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
CDC	Center for Disease Control
IU	International unit
NHANES	National Health and Nutrition Examination Survey
UV	Ultraviolet

1.1 Vitamin D: yesterday

To fully appreciate the current and future implications of vitamin D insufficiency, we must explore its historical context. Historically vitamin D deficiency was defined by the clinical recognition of rickets, the childhood disease of impaired skeletal development, or osteomalacia in adults. The first descriptions of clinical manifestations of rickets appeared in ancient times. Second century Roman physician Soranus published a text in which he recommended swaddling to prevent deformities common in city dwellers (Foote, 1927; Rajakumar, 2003). Modern scientists examined a pediatric skull and radius from pre-Columbian Peru and found both consistent with rickets. In the 1920s John Foote examined fifteenth century paintings from the Netherlands and Germany and concluded that the infant subjects showed evidence of rickets (Foote, 1927).

The term 'rickets' first appeared in 1634 when listed as a cause of death in London's Annual Bill of Mortality (O'Riordan, 2006). Four publications regarding rickets appeared in the mid-seventeenth century: Daniel Whistler's doctoral defense thesis (O'Riordan, 2006; Smerdon, 1950), Arnold Boote's chapter in his book 'Medical Observations on Neglected Ailments', Francis Glisson' book which described findings seen on post mortem examinations and John Mayow's book. For the next century and a half, little occurred in regards to rickets in the medical community (O'Riordan, 2006).

Investigators began studying the potential relationships between rickets and both cod liver oil and sunlight in the early 19th century. Unpublished rumors and subsequent case reports began spilling out of Holland, Germany and France: The Society of Science and Arts of Utrecht described the therapeutic properties of cod liver oil in 1822 (Guy, 1923); German physician Schutte published a 25 year case history of his successes in curing rickets with cod liver oil in children in 1824 (Guy, 1923); and French physician Bretonneau reported successfully treating a 15 month old suffering from rickets in 1827 (Holick, 1994; Rajakumar, 2003).

Scientists also observed a relationship with sunlight. In 1822 Sniadecki noted a higher incidence of rickets in children living in Warsaw than children living in surrounding rural communities; he blamed inferior sunlight exposure within the city as the causative factor (Holick, 1994; 2003). In 1838 Jules Guerin experimented on puppies: he weaned puppies to a dark basement and fed them raw meat while the littermates remained in a normal environment. He reported the basement

puppies 'looked sad', vomited, and developed misshapen limbs and other signs of rickets while the other pups had no such signs (Mayer, 1957). Hugh Owen Thomas treated rachitic children with sunlight exposure on hospital balconies in Wales in 1878 (Chesney, 2012). While on a medical mission in Japan, Theobald Palm noted the absence of rickets. He collected prevalence data from worldwide missionaries and noted that areas of temperate latitude or heavier air pollution had more cases or rickets but that even filthy areas of the jungle did not; he concluded sunlight as the protective factor. August Hirsch and the Investigation Committee on the British Medical Association developed similar maps but blamed overcrowding and air/soil conditions (Chesney, 2012; Holick, 2003). Finally, John Bland-Sutton observed monkeys and lions in glass enclosures at the London Zoo and noted development of rickets within months of the animals' arrivals or births. However, he noted that lion cubs receiving cod liver oil and crushed bones to their usual lean-meat diet recovered from their rickets-features. He hypothesized dietary fat cured rachitic features (Findlay, 1908; Mayer, 1957; O'Riordan, 1997; Park, 1923; Rajakumar, 2003).

By the turn of the 20th century, speculations regarding the etiology of rickets varied: syphilis, scurvy, genetics, acidosis causing bony decalcification, strep infection, confinement/exercise deprivation, over-eating, or disorders of the thymus, thyroid, adrenal, parathyroid, or carotid (Cheadle, 1988; Findlay, 1908; Park, 1923). Studies of scurvy, beri-beri, and pellagra led to the discovery of 'vital substances' (later 'vitamins') which, in deficiency, led to disease. (Chesney, 2012) At this same time, rickets had become epidemic in the US and Europe: autopsy studies identified rickets in 80-96% childhood deaths (Holick, 1994; Park, 1923; Rajakumar, 2003), oral exams in London school children saw rickets in the teeth of 80% (Mellanby, 1919), and estimates of children living in industrialized cities exceeded 90% (Holick, 2003). Women with pelvises flattened by the affects of childhood rickets began requiring Cesarean births (Holick, 2003).

The early 1900s represented a turning point in rickets research. In terms of light-related work, Buchholz, Schmorl, Hess, Lundagen and Raczynski all noted seasonal variations in the incidence of rickets (Chesney, 2012; Park, 1923). German pediatrician Kurt Huldchinsky treated over 100 cases of childhood rickets with quartz mercury-vapor lamp UVB irradiation and then noted that UVB exposure to a single limb produced X-ray evidence of full skeletal healing (Chesney, 2012; Holick, 1994; 2003; Park, 1923; Rajakumar, 2003). Harriett Chick and her colleagues treated children with rickets at a Vienna hospital after World War I. They treated children with nothing, mercury-vapor lamp UVB exposure, sunlight, cod liver oil, or a combination of UVB and cod liver oil. They found several interesting results: healing rates depended on amount of UVB exposure; partial body UVB exposure produced full body healing; no new cases of rickets developed during the summer months in any group; and most rapid healing occurred in children receiving both UVB exposure and cod liver oil (Chick *et al.*, 1922; O'Riordan, 1997). Additionally Hess studied epiphyses calcification on radiography and published that irregular sunlight exposure, in the absence of diet fortification, improved rickets (Hess and Mildred, 1925b; Holick, 1994).

From a diet-perspective, English physician Edward Mellanby varied the diets of puppies and noted the protective factor of cod liver oil, butter and whole milk. He postulated poor intake of 'an antirachitic factor which is either fat-soluble A or has a somewhat similar distribution to the

fat soluble A' as the cause of rickets (Mellanby, 1919). Elmer McCollum, John Holand, Edward Park and Paul Shipley induced rickets in rats and then healed those manifestations with cod liver oil. They then oxidized cod liver oil to isolate the anti-xerophthalmic and anti-rachitic properties and in 1922 they deduced that the two factors were distinct (McCollum *et al.*, 1921, 1922). They postulated that this factor was a vitamin and, as the fourth vitamin discovered, named it vitamin D (Holick, 1994; McCollum *et al.*, 1921, 1922; Rajakumar, 2003). Two research groups (Hess and Weinstock, Steenbock and Black) noted that previously anti-rachitic-deficient foods would gain anti-rachitic activity when irradiated with UV light (Hess, 1924; Hess and Mildred, 1925a; Holick, 1994; Steenbock, 1924). University of Wisconsin's Harry Steenbock not only published his findings regarding the ability to impart anti-rachitic factor to rat feed via UV irradiation, but patented the process 'to protect the interest of the public in the possible commercial use of these findings' (Schneider, 1973; Steenbock, 1924; Steenbock and Black, 1924; Steenbock and Nelson, 1924). The University created a board of trustees to manage the patent. Quaker Oats attempted to purchase exclusive rights, but Steenbock and the board refused. They sold licenses to Quaker Oats for cereal fortification and to a pharmaceutical agency to develop Viosterol (medicinal vitamin D supplementation). They refused to sell licenses to manufacturers of chewing gum, tobacco, lipstick, beer or soft drinks, deciding that only healthy foods should receive fortification. With dairy-farmer roots, Steenbock also developed a process to fortify milk. Laws at the time prohibited any additives to milk; three manufacturers developed equipment to irradiate flowing films of milk. (Wisconsin Alumni Research Foundation)[1] Initially milk was supplemented to 400 IU of vitamin D per liter, the same amount of vitamin D in one teaspoon of cod liver oil (Chesney, 2012). This process of fortification revolutionized the prevention of rickets (Wisconsin Alumni Research Foundation).

The next boom in vitamin D research started in the 1960s. Researchers at the University of Wisconsin isolated a metabolite chromatographically-distinguishable from vitamin D3, subsequently determined its structure as 25-hydroxyvitamin D (25(OH)D) and discovered it was produced in the liver (Blunt *et al.*, 1968; Norman *et al.*, 1964; Ponchon and DeLuca, 1969). They found a third distinct metabolite (Haussler *et al.*, 1968; Lawson *et al.*, 1969) and researchers in Cambridge, after determining production occurred in the kidney, diagramed our modern understanding of vitamin D synthesis and metabolism (Fraser and Kodicek, 1970). In 1971 three separate labs (University of Wisconsin, Cambridge and University of California) confirmed the structure of this metabolite as $1,25(OH)_2D$ (Holick *et al.*, 1971; Lawson *et al.*, 1971; Macintyre *et al.*, 1977; Norman *et al.*, 1971). Scientists re-classified vitamin D as a hormone and not a true vitamin (Holick, 1994). In 1979 Stumpf published results of ^3H nuclear localization in rats that showed vitamin D receptors in the stomach, parathyroid, gonads, brain and skin. Subsequent studies found vitamin D receptors in a plethora of other body tissues (Holick, 1994; Stumpf *et al.*, 1979). Finally, in 1980, Holick described the dermal synthesis of vitamin D (Holick *et al.*, 1980).

[1] Wisconsin Alumni Research Foundation, Steenbock and WARF's Founding. Available at: http://www.warf.org/about/index.jsp?cid=26&scid=33. Accessed 5/25/2012.

1.2 Vitamin D: today

1.2.1 Modern understanding of vitamin D metabolism

As the 19th century scientists suspected, both diet and skin exposure to UVB provide vitamin D. It occurs naturally in few foods, namely fatty, ocean dwelling fish (salmon, sardines, mackerel, tuna, and cod), shiitake mushrooms and egg yolks. It is also fortified in some cereals (100 IU/serving), milks (100 IU/227 g), orange juice (100 IU/227 g), butters (50 IU/99 g), margarines (430 IU/99 g), cheeses (100 IU/85 g) and yogurts (100 IU/227 g). (Holick, 2007) Vitamin D exists in two forms: D2 (ergocalciferol), which is produced via irradiation of yeast, and D3 (cholecalciferol), which is the form found in fatty fish and from dermal synthesis following UV exposure (Holick, 2006). As scientists deduced in the 1960s, regardless of the source, the parent compound is metabolized to 25(OH)D (calcidiol) in the liver and then further metabolized to $1,25(OH)_2D$ (calcitriol) in the kidney. The $1,25(OH)_2D$ is the active hormone that acts on vitamin D receptors throughout the body.

1.2.2 Defining vitamin D deficiency... not as easy as it sounds

Today, the definition of vitamin D deficiency has expanded from the clinical diagnosis of rickets to a definition based on the serum concentration of 25(OH)D. However, this is an imperfect marker, because it represents vitamin D supply rather than vitamin D function. The 25(OH)D metabolite has no physiologic function, and its conversion to active $1,25(OH)_2D$ is tightly regulated. Rickets or osteomalacia typically occur with serum 25(OH)D values <10 ng/ml (1.0 ng/ml = 2.5 nmol/l) (Thacher and Clarke, 2011). Optimal bone health and other non-skeletal benefits may be gained from 25(OH)D concentrations greater than those necessary to prevent rickets and osteomalacia. Currently, no universal standard definition of vitamin D deficiency exists. The most common definitions include: deficiency <20 ng/ml (<50 nmol/l), insufficiency 20-30 ng/ml (50-75 nmol/l) and sufficiency >30 ng/ml (>75 nmol/l) (Heaney and Holick, 2011; Holick, 2007), or deficiency <12 ng/ml (<30 nmol/l), insufficiency 12-20 ng/ml (30-50 nmol/l) and sufficiency >20 ng/ml (>50 nmol/l) (Institute of Medicine, 2011).

However, the clinical utility of the term 'insufficiency' is not at all clear. Because the functional effect of a given 25(OH)D value is widely variable, it is likely that the range defined as insufficiency represents adequate vitamin D status for some and deficiency for others. The requirement for vitamin D appears to be lower when the calcium intake is adequate. Definitions of insufficiency have been based on analysis of parathyroid suppression and/or calcium absorption. Some have argued that parathyroid suppression reaches a plateau at mean 25(OH)D concentrations of 28-40 ng/ml. However, flaws of these studies included substantial individual variation, lack of a clear inflection point, and exclusion of children (Heaney, 2004; Holick, 2007; Lee *et al.*, 2008; Thacher and Clarke, 2011). Calcium absorption has been reported to plateau at a mean 25(OH)D concentration of 32 ng/ml. However, additional studies fail to show a relationship between serum 25(OH)D concentrations and intestinal calcium absorption, except at concentrations below 5 ng/

ml (Heaney, 2004; Holick and Chen, 2008; Need *et al.*, 2008; Thacher and Abrams, 2010; Thacher and Clarke, 2011).

1.2.3 Return of rickets to a modern society

Following routine fortification of foods with vitamin D, the incidence of rickets declined dramatically, and it was considered rare by the 1960s. However, a recent worldwide resurgence of rickets has been recognized (Thacher *et al.*, 2006). Best estimates of national prevalence come from chart reviews and case report series since rickets is not a reportable disease (Nield *et al.*, 2006). Estimates range from 6-9 cases per million hospitalized children in the US (Centers for Disease Control and Prevention, 2001; Scanlon, 2001) or Canada (Ward *et al.*, 2007). Additionally, meta analyses of published cases found 166 cases (in 22 studies) 1986-2003 (Weisberg *et al.*, 2004) and 65 cases (in 11 studies) 1975-1985 (Cosgrove and Dietrich, 1985). The CDC has expressed concern regarding the prevalence of rickets, especially among darkly pigmented children (Scanlon, 2001).

1.2.4 Prevalence of hypovitaminosis D

Estimates of worldwide vitamin D deficiency exceed 1 billion individuals (Bell, 2011; Holick, 2007; Makariou *et al.*, 2011). In the USA, NHANES reported overall national mean serum concentrations of 25(OH)D at 30 ng/ml in 1988-1994 (Ginde *et al.*, 2009a), 24 ng/ml in 2001-2004 (Ginde *et al.*, 2009a) and 19.9 ng/ml in 2005-2006 (Forrest and Stuhldreher, 2011). International studies show mean 25(OH)D values of 8.2 ng/ml in Iranian adults (Van Schoor and Lips, 2011); 14 ng/ml in veiled and 17.2 ng/ml in non-veiled African women in Tunisia (Van Schoor and Lips, 2011); and 11-12.8 ng/ml in Middle Eastern university students living in Riyadh (Sedrani, 1984). A British study sampled 45 year old adults from a birth cohort and found winter values below 10, 16 and 20 ng/ml in 15.5, 46.6% and 87.1% respectively (Hypponen and Power, 2007).

Several studies address postmenopausal women, given their risk of osteoporosis. The prevalence of vitamin D deficiency (25(OH)D<30 ng/ml) was 50% in Thailand and Malaysia, 75% in the USA and 90% in Japan and South Korea (Dawson-Hughes *et al.*, 2010). In the UK, South Asian immigrants and Caucasian natives possessed mean serum concentrations of only 4.3 and 16.3 ng/ml respectively (Lowe *et al.*, 2010). Italian investigators found values less than 12 ng/ml and 5 ng/ml in 76% and 27% of women, respectively (Isaia *et al.*, 2003).

Children require vitamin D to establish optimal bone density during growth. Projections based on data from NHANES 2001-2004 suggested deficiency (<15 ng/ml) in 7.6 million US children and insufficiency (15-29 ng/ml) in another 50.8 million children (Kumar *et al.*, 2009). Other studies have shown deficiency (<20 ng/ml) in 48% of healthy Maine girls ages 9-11 at some point during a three year study (Sullivan *et al.*, 2005), 12.1% of healthy Boston infants and toddlers (Gordon *et al.*, 2008), and 42% of Boston adolescents (with 24.1% <15 ng/ml and 4.6% <8 ng/ml) (Gordon *et al.*, 2004). Mean serum concentrations of 11.8 ng/ml (with 35.7% below 9 ng/ml) in New Delhi children (Marwaha *et al.*, 2005), 17 ng/ml in Lebanese youth in the spring (El-Hajj

Fuleihan *et al.*, 2001), and 5 ng/ml in Chinese female adolescents (Van Schoor and Lips, 2011) have been reported.

Vitamin D deficiency also affects men. A study of community-dwelling men in several USA cities revealed a mean serum concentration of 25.1 ng/ml with 71.1% of participants below 30 ng/ml, 25.7% below 20 ng/ml and 2.9% below 10 ng/ml (Orwoll *et al.*, 2009).

Hypovitaminosis D even extends into sunny climates. A study that recruited healthy high-sun-exposure participants from a surf shop in Honolulu Hawaii found 51% of study participants' serum concentrations of 25(OH)D below 30 ng/ml (Binkley *et al.*, 2007). Similarly children in Texas showed serum levels <12, 20 and 32 ng/ml in 1%, 16% and 68% of participants, respectively (Rovner and O'Brien, 2008).

Those with sub-par health commonly possess low values. Medical inpatients at Massachusetts General Hospital were found to have a mean serum concentration of 15 ng/ml with 57% below 15 ng/ml and 22% below 8 ng/ml (Thomas *et al.*, 1998). Estimates of vitamin D deficiency in the non-institutionalized elderly range from 40 to 100% (Holick, 2007). A study of elderly individuals >98 years found undetectable serum values in 95% (Passeri *et al.*, 2003).

Finally, post partum women and their infants often have serum 25(OH)D concentrations shortly after birth below 15 ng/ml (Taha *et al.*, 1984). Prevalences of deficiency have been reported at 50% (mothers <20 ng/ml) (Lee *et al.*, 2007), 65% (Boston newborns <12 ng/ml) and 45.6% (black Pittsburgh newborns <15 ng/ml) (Rovner and O'Brien, 2008). Due to the low vitamin D content of breast milk, breastfeeding has been identified as a risk factor for vitamin D deficiency. One study found 48% of mothers and 43% of babies with 25(OH)D values <10 ng/ml (Seth *et al.*, 2009).

1.2.5 Why has this become a problem again?

Several factors may contribute to the prevalence of hypovitaminosis D and the resurgence of rickets in our modern society.

A variety of medical conditions interfere with vitamin D absorption (i.e. celiac disease, cystic fibrosis, Crohn's disease, or gastric bypass surgery), hepatic conversion or renal synthesis of vitamin D metabolites (Tsiaras and Weinstock, 2011). Medications, including anticonvulsants, glucocorticoids, antiretrovirals, and antirejection drugs can interfere with vitamin D metabolism (Holick, 2007).

The prevalence of obesity has increased throughout the world, and fat soluble vitamin D is sequestered in adipose tissue. A study evaluated serum levels of 25(OH)D in obese and ideal-weight-matched-controls either 24 hours after whole body UV irradiation or oral ingestion of 50,000 IU vitamin D2. Basal values between groups were similar, but the amount of increase in the nonobese subjects was 57% higher (15.3 versus 6.7 ng/ml) after UVB irradiation. Body mass

index was inversely correlated with serum concentrations after either UVB irradiation or oral ingestion (Wortsman *et al.*, 2000).

Several barriers exist that prevent adequate sunlight exposure. Recommendations regarding skin cancer promote sun avoidance and sunscreen use. When used properly, sunscreen with SPFs of 8 or 15 reduce cutaneous vitamin D synthesis by 97.5% and 99% respectively (Holick, 2003; Holick and Chen, 2008; Scanlon, 2001). Para-aminobenzoic acid (a sunscreen) applied to human epidermis blocked production of vitamin D with UV exposure compared with marked production of vitamin D in para-aminobenzoic acid-free epidermis samples (Matsuoka *et al.*, 1987). A study of sunscreen users and non-users with equivalent sunlight exposure revealed significantly lower serum 25(OH)D concentrations in sunscreen users (16.8 ng/ml versus 36.5 ng/ml) (Matsuoka *et al.*, 1988). Additionally, pollution impedes cutaneous vitamin D synthesis from sunlight. Black carbon from biomass and fossil fuel combustion absorbs UVB radiation from sunlight and decreases the amount that reaches the earth's surface by approximately 5% in typical urban environments (Highwood and Kinnersley, 2006) and up to 81% in the Brazilian rain forests (Mims, 1996).

The seasonal tilt of the earth can impact the amount of UVB available for cutaneous vitamin D synthesis. An appropriate zenith angle is required for UVB to penetrate the non-polluted ozone. Latitudes above 35°N and below 35°S produce too oblique of an angle during winter months for UVB penetration (Holick, 2003). This produces almost complete cessation of cutaneous vitamin D synthesis seasonally in some parts of the world: Rome (41.9°N) November through February (Tsiaras and Weinstock, 2011), Berlin (52.5°N) October through April (Tsiaras and Weinstock, 2011), Boston (42°N) November through February (Webb *et al.*, 1988), Edmonton Canada (52°N) mid-October through mid-April (Holick, 1994; Webb *et al.*, 1988).

Purdah, cultural covering, limits sunlight exposure and cutaneous vitamin D synthesis, even in the sunniest areas of the world (Holick and Chen, 2008). Window-glass blocks all UVB, eliminating any benefit for those who remain indoors (Cannell and Hollis, 2008). Melanin in the epidermis of darkly pigmented skin reduces vitamin D synthesis (Aloia, 2011). Finally, advancing age decreases cutaneous 7-dehydrocholesterol necessary for synthesis of vitamin D (Holick, 2003; Holick and Chen, 2008; Holick *et al.*, 1989; MacLaughlin and Holick, 1985).

Fortification revolutionized the world's approach to vitamin D deficiency. However, levels of fortification can vary significantly. For instance, fortified milk is advertised to contain 400 IU of vitamin D per quart. However, a study of randomly selected milk found that only 29% of the samples tested contained 320-480 IU/quart, 50% of samples contained <80% of advertised amount, 14% contained <5% advertised amount and 21% of the skim milk samples contained no detectable vitamin D (Holick, 1994; Holick *et al.*, 1992; Scanlon, 2001). A four year study in New York found that only half of sampled milk complied with label declarations (Murphy *et al.*, 2001; Yetley, 2008).

Few foods naturally contain vitamin D. Ocean-dwelling salmon contains 600-1000 IU/99 g. However, canned salmon contains 300-600 IU/99 g and farmed salmon contains only 100-250 IU/99 g (Holick, 2007).

Finally, breastfeeding has played a role. HealthyPeople 2010 set a goal for 75% of infants to breast-feed for the first six months of life (US Department of Health, 2000). Between 1988 and 1999, breastfeeding among African American mothers in North Carolina increased from 5.2% to 34.7%. During this interval several cases of rickets were identified in the same region. Breast milk has low concentrations of vitamin D; therefore, the American Academy of Pediatrics recommends universal supplementation of vitamin D to exclusively breastfed infants. However, compliance with this recommendation is poor. Data regarding supplementation of lactating mothers is somewhat new and not ready for universal recommendations (Scanlon, 2001).

1.2.6 Supplementation regimens

Significant controversy exists regarding optimal supplementation dosing; partly related to the lack of universally accepted optimal serum values. Additionally, while D2 and D3 supplements both increase in 25(OH)D values, D3 has produced slightly superior results, suggesting a higher dose of D2 needed to achieve similar serum 25(OH)D concentrations (Binkley *et al.*, 2011). Finally, the variety of dosing regimens is confusing. A review of 306 patients with vitamin D insufficiency at an Atlanta VA revealed 36 different oral vitamin D prescribing regimens. Doses ranged from 400 to 50,000 IU given twice daily to once monthly. The three most commonly utilized regimens (50,000 IU weekly ×4, then monthly ×5; 50,000 IU monthly ×6; 50,000 IU three times weekly ×6 weeks) all increased the serum 25(OH)D concentration but only achieved concentrations >30 ng/ml in 38%, 42% and 82% of subjects respectively. No toxicities were reported for any regimen (Pepper *et al.*, 2009). Each additional 100 IU (2.5 μg) increment of daily oral vitamin D3 increases serum 25(OH)D by about 1 ng/ml (0.6-1.2 ng/ml = 1.5-3 nmol/l) (Barger-Lux *et al.*, 1998; Dawson-Hughes *et al.*, 2010; Heaney, 2004).

With support from the United States and Canadian governments, the Institute of Medicine updated the Dietary Reference Intakes for calcium and vitamin D in 2011. The committee concluded that neither adequate evidence regarding the cause/effect outcomes nor the dose-response relationship currently exists for vitamin D; therefore, they made recommendations solely based on bone health. The recommended RDAs strive to achieve >20 ng/ml 25(OH)D in >97.5% of the population: 600 IU daily in ages 1-70 years (including pregnant and lactating women) and 800 IU daily in elderly (>70 years). The tolerable upper intake level was set at 4,000 IU/day for individuals >9 years. The committee agreed that neither toxicity nor hypercalcemia has been reported for daily intakes <10,000 IU; however, lower values were chosen due to lack of data regarding outcomes with chronic intake. The committee stated that additional research, including better understanding of serum biomarkers, is urgently needed (Aloia, 2011; Institute of Medicine, 2011; Ross *et al.*, 2011).

Many within the medical and research community expressed surprise at these recommendations, since several studies suggest benefit with higher doses. One study estimated a daily need of 3,440 IU for the population to achieve 30 ng/ml serum concentrations. This estimate utilized computer simulation based on data from a six month study of racially diverse adults receiving oral vitamin D supplementation with dosing adjustments performed every two months (Aloia *et al.*, 2008). Another study compared either 1,600 IU daily or 50,000 IU once monthly in community dwelling adults >65 years. None developed toxicity but 19% failed to achieve serum concentrations >30 ng/ml after one year of supplementation (Binkley *et al.*, 2011). Studies regarding fracture prevention have identified an optimal serum concentration of 28-40 ng/ml. Various studies have estimated 700-1000 IU daily for the average elder to achieve this goal; however, much higher doses may be necessary for the entire elder population to achieve these concentrations (Dawson-Hughes, 2004; Dawson-Hughes *et al.*, 2010).

The intramuscular route can also be utilized: ergocalciferol 15 mg IM has been used to treat osteomalacia (Burns and Paterson, 1985).

1.2.7 Serum 25(OH)D measurement

Reported values differ when tested in different laboratories and with different methodologies. Not all labs detect both the 25(OH)D2 and 25(OH)D3 forms. One study sent twenty samples from ten healthy subjects to six laboratories. Each subject contributed one basal sample and one sample spiked with an additional 20 ng/ml 25(OH)D. The labs reported basal sample means of 25(OH)D ranging from 17.1-35.6 ng/ml. The mean increase detected in the samples spiked with 20 ng/ml of additional 25(OH)D ranged from 7.7-18 ng/ml. Individual variation for a single sample between labs ranged from 10-40 ng/ml (Binkley *et al.*, 2004).

Two organizations are working to improve accuracy of testing: The National Institute of Standards and Technology introduced internal standards and the Vitamin D External Quality Assessment Scheme works with analysis problems in individual laboratories (Aloia, 2011).

1.3 Vitamin D: tomorrow

1.3.1 Beyond bone health

The vital role of vitamin D in bone health is universally accepted. However, a plethora of publications over the past several years shows that the role of vitamin D extends far beyond the skeleton. The future of vitamin D will be determined by establishing the non-skeletal benefits of vitamin D and individualizing vitamin D recommendations based on functional outcomes and disease risk. Vitamin D receptors are widely distributed throughout the body, as is the 1α-hydroxylase enzyme responsible for converting 25(OH)D to $1,25(OH)_2D$. Observational data have demonstrated relationships between vitamin D status and infectious, immune, metabolic, degenerative, and neoplastic diseases.

Both strength (see Chapter 6) and falls (see Chapter 4) improve with vitamin D sufficiency. Studies have shown a positive correlation between muscle strength and serum 25(OH)D concentrations in elderly subjects (Bischoff-Ferrari *et al.*, 2004; Holick, 2007; Visser *et al.*, 2003). Other studies have shown less falls with vitamin D intake >600-800 IU/day (Bischoff-Ferrari *et al.*, 2009; Broe *et al.*, 2007; Dawson-Hughes *et al.*, 2010; Holick, 2007; Mason *et al.*, 2011; Murad *et al.*, 2011; Thacher and Clarke, 2011). Although osteomalacia, a painful bony condition, has become rare, non-specific pain is associated with hypovitaminosis D (93% patients with musculoskeletal/bone pain had 25(OH)D <20 ng/ml) (Holick, 2007; Plotnikoff and Quigley, 2003; Thacher and Clarke, 2011).

Observational studies show an inverse relationship between serum concentrations of 25(OH)D and death (Ginde *et al.*, 2009b; Makariou *et al.*, 2011; Thacher and Clarke, 2011; Zittermann *et al.*, 2012). Additionally, subjects taking a vitamin D supplement have decreased mortality compared with controls (Autier and Gandini, 2007; Bjelakovic *et al.*, 2011; Cannell and Hollis, 2008; Makariou *et al.*, 2011; Nadir *et al.*, 2010; Scragg *et al.*, 2007; Thacher and Clarke, 2011).

Vitamin D may have cardiovascular benefits. Observational studies found slightly lower blood pressure in individuals with higher serum 25(OH)D concentrations (Forman *et al.*, 2007; Lind *et al.*, 1995; Makariou *et al.*, 2011; Nadir *et al.*, 2010; Reis *et al.*, 2009; Scragg *et al.*, 2007). Two studies have shown a 9% decrease in systolic blood pressure with initiation of supplemental vitamin D (Islam *et al.*, 2011; Judd *et al.*, 2010; Pfeifer *et al.*, 2001). However, a meta-analysis of 8 studies showed a nonsignificant reduction in SBP and a small but statistically significant decrease in diastolic blood pressure (Witham *et al.*, 2009). The WHI failed to show any blood pressure improvement, but the low compliance of 59% and the low dose of vitamin D may have impacted results (Margolis *et al.*, 2008). Hypertensive individuals exposed to tanning beds became normotensive in 3 months while their serum 25(OH)D concentrations increased >180% (Krause *et al.*, 1998). This relationship may be due to $1,25(OH)_2D$ regulation of the renin-angiotensin system (Li *et al.*, 2002). Although data do not agree, several studies have shown a beneficial relationship between vitamin D adequacy and improved cholesterol values (Carbone *et al.*, 2008; Ford *et al.*, 2005; Hypponen *et al.*, 2008; Lind *et al.*, 1995; Makariou *et al.*, 2011; Martins *et al.*, 2007). NHANES observational data (Kendrick *et al.*, 2009; Kim *et al.*, 2008; Makariou *et al.*, 2011) and a German prospective study (Makariou *et al.*, 2011; Pilz *et al.*, 2008) have both suggested increased risk of cardiovascular disease including stroke or death from congestive heart failure with vitamin D insufficiency. Additional observational studies have demonstrated a relationship between coronary artery disease (Grandi *et al.*, 2010; Kim *et al.*, 2008; Makariou *et al.*, 2011; Temmerman, 2011) or cardiovascular death (Dobnig *et al.*, 2008; Ginde *et al.*, 2009b; Temmerman, 2011; Thacher and Clarke, 2011) and vitamin D insufficiency.

Vitamin D may play a role in both type 1 and type 2 diabetes. A 31-year prospective study of Finish infants given 1000 IU daily for the first year of life (Hypponen *et al.*, 2001) and a meta-analysis of observational studies of children ever receiving vitamin D supplements (Zipitis and Akobeng, 2008) showed a lower risk of development of type 1 diabetes. Additional studies have shown potentially beneficial relationships between vitamin D and type 2 diabetes (Borissova *et*

al., 2003; Chiu *et al.*, 2004; Gannage-Yared *et al.*, 2009; Lind *et al.*, 1995; Nadir *et al.*, 2010; Pittas *et al.*, 2006, 2007a,b; Schwalfenberg, 2008).

The kidney, the site of conversion from 25(OH)D to $1,25(OH)_2D$, is also impacted by vitamin D (see Chapter 11). A meta-analysis showed improved survival in chronic kidney disease patients with higher 25(OH)D serum concentrations (Pilz *et al.*, 2011). NHANES data showed increased prevalence in albuminuria in healthy adults with lower concentrations of serum 25(OH)D (De Boer *et al.*, 2007). Treatment with paricalcitol (a synthetic analog of $1,25(OH)_2D$) decreased proteinuria in patients with chronic kidney disease (Agarwal *et al.*, 2005; Alborzi *et al.*, 2008).

Some have suggested that the seasonality of respiratory infections is related to wintertime hypovitaminosis D (Cannell *et al.*, 2006). An observational study of young Finnish men on a military base found that those with low 25(OH)D serum concentrations (<16 ng/ml) had more absences secondary to respiratory infections (Laaksi *et al.*, 2007). A randomized trial in Japanese schoolchildren showed a reduced incidence of influenza A in those randomized to receive 1200 IU D3 daily compared with those given placebo (Urashima *et al.*, 2010).

Several cross sectional studies reported correlations between serum 25(OH)D concentrations and mood (Bertone-Johnson, 2009). A randomized controlled trial showed significant improvement in mood after one year of vitamin D treatment (Bertone-Johnson, 2009; Jorde *et al.*, 2008). The Finnish birth cohort also showed a decreased incidence in diagnosis of schizophrenia by age 31 in subjects who received vitamin D supplementation during the first year of life (McGrath *et al.*, 2004).

The potential relationships between vitamin D status and neurological conditions including dementia, epilepsy (see Chapter 30), and multiple sclerosis (see Chapter 25) are also of interest. Studies have suggested a decreased risk of multiple sclerosis with vitamin D supplementation (Munger *et al.*, 2004), improved 25(OH)D serum concentrations (Munger *et al.*, 2006; Van Amerongen *et al.*, 2004) or UV exposure. Additionally, a study of 12 patients with multiple sclerosis treated with oral vitamin D supplementation for 28 weeks showed a decrease in gadolinium enhancing lesions on nuclear magnetic brain scan (Kimball *et al.*, 2007). However, another study of 23 individuals randomized to either 6,000 IU or 1000 IU D_2 daily showed no differences in magnetic resonance imaging endpoints after six months (Stein *et al.*, 2011).

The relationship of vitamin D with several different cancers has been investigated. A PubMed search revealed almost 2,000 papers published in the past decade with the medical subject headings terms 'vitamin D' and 'neoplasm'. Research includes cancers of the prostate (see Chapter 23), ovary, lung, pancreas (see Chapter 21), skin, esophagus (see Chapter 24), stomach, endometrium, kidney, and blood with the strongest literature showing a potential benefit for cancers of the breast (Chen *et al.*, 2010; Garland *et al.*, 2007; Gissel *et al.*, 2008; Grant, 2010; World Health Organization International Agency for Research on Cancer, 2008) and colorectum (Fedirko *et al.*, 2010; Gandini *et al.*, 2011; Gorham *et al.*, 2005; 2007; Grant, 2010; Lee *et al.*, 2011;

Ma *et al.*, 2011; Wei *et al.*, 2008; World Health Organization International Agency for Research on Cancer, 2008; Yin *et al.*, 2009; 2011).

Topical $1,25(OH)_2D$ preparations have become firmly established as effective treatment for psoriasis. Additionally, oral $1,25(OH)_2D$ has shown improvement in both skin manifestations and the joint pain of psoriatic arthritis (Holick, 1994; 2007).

The health implications of vitamin D status in pregnant and lactating mothers and their infants are actively being investigated. A case-control study of pregnant women showed a dose-response relationship between serum 25(OH)D and eventual risk of pre-eclampsia during pregnancy (Bodnar *et al.*, 2007).

1.3.2 Personalized medicine

The future of vitamin D will likely bring with it a more individualized approach to assessing vitamin D status and needs. Currently, vitamin D sufficiency is determined by a marker of storage, 25(OH)D. However, there is likely wide individual variation in the functional implications of a given level of 25(OH)D. Furthermore, a fixed amount of vitamin D intake or sun exposure produces a wide individual variation in 25(OH)D response (Aloia *et al.*, 2008; Heaney *et al.*, 2003). Even when all the factors known to influence 25(OH)D concentrations are accounted for, most of the individual variation of 25(OH)D values is difficult to explain. This variation is partially explained by genotypic variants of the vitamin D binding protein, vitamin D receptor, and the hydroxylase enzymes of the vitamin D metabolic pathway (Ahn *et al.*, 2010; Wang *et al.*, 2010). With more widespread use of genotypic analysis, it may be possible to personalize an individual's vitamin D requirement, particularly in view of other disease risk factors. A vitamin D 25-hydroxylase genetic variant has been associated with the risk for type 1 diabetes mellitus (Ramos-Lopez *et al.*, 2007). Genetic variants of the vitamin D receptor may modulate the individual response to vitamin D. Subjects with osteoporosis who showed a response to supplemental calcium and vitamin D expressed a difference in the vitamin D receptor polymorphisms compared with those who did not respond (Elnenaei *et al.*, 2011).

Additional markers of the functional response to vitamin D at the individual level may be more readily available in the future and permit predicting and monitoring the effect of vitamin D supplementation. Measurement of the physiological effects of vitamin D that relate to bone metabolism, the immune system, or other effectors of disease could allow tailoring of the dose of vitamin D to attain maximal physiological benefit. As randomized controlled trials become available confirming the benefits of vitamin D in non-skeletal diseases, the recommended intake of vitamin D and optimal 25(OH)D concentration may need to be adjusted to account for these outcomes. The recommended vitamin D intake may require adjustment for calcium intake, body size, body fat, ethnicity, and usual sun exposure. As individualized medicine becomes more of a reality in all areas of medical care, the optimal role of vitamin D will certainly be better defined.

1.3.3 So much more to learn!

Although our knowledge of vitamin D has grown exponentially since ancient descriptions of rickets, many questions remain. Individuals and organizations have posed several questions still needing to be answered.

In October 2011, scientists, government agents, and academics, including representatives from the CDC and American Academy of Pediatrics, gathered for 'A Vitamin D Expert Panel Meeting' to examine current knowledge and future research needs. They stressed that public health recommendations should consider health implications beyond rickets and that more longitudinal studies are needed (Scanlon, 2001).

Similarly, National Institute of Health held a conference entitled 'Vitamin D and health in the 21st century: bone and beyond' in 2003. Along with the National Institute of Health members, participants included representatives from national institutes (National Cancer Institute, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Diabetes and Digestive and Kidney Disorders), government departments (Department of Agriculture, Office of Dietary Supplements, CDC) and industry (National Dairy Council, Coca-Cola). They identified several important areas in need of research including developing universal definitions of adequacy based on health outcomes, determination of dietary/supplement/UV requirements including better understanding of safety and toxicity in all ages and ethnic groups (Raiten and Picciano, 2004).

Vitamin D has exciting potential, and a flurry of research activity is now underway to explore its potential benefits. Enthusiasm regarding vitamin D is reminiscent of the health benefits attributed to other vitamins in the past, many of which were not eventually confirmed. Vitamin D differs from other vitamins in that it is a prohormone and not a true vitamin. The future is bound to bring clarification of the optimal role of vitamin D and new applications for vitamin D in health and disease.

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