Vitamin D insufficiency and musculoskeletal health in children and adolescents

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Abstract. A large body of data demonstrates a high prevalence worldwide of hypovitaminosis D in children and adolescents, at a critical time of bone mass accrual. Increasing evidence supports a deleterious effect of vitamin D insufficiency on musculoskeletal health in this age group based on cross-sectional studies, studies relating vitamin D to biochemical variables in the homeostatic pathway for vitamin D physiology (PTH, calcitriol, bone remodeling). Two recent randomized interventional trials show that vitamin D supplementation increases accrual of bone mass in girls, and this is partly explained by enhanced calcium absorption and bone mineralization. However, recent data also suggest beneficial effects on lean mass and bone geometry. It remains uncertain whether the beneficial effects of vitamin D in girls are reflected in the peak bone mass they eventually attain. A desirable 25(OH) D level to optimize musculoskeletal health in girls seems to be between 30 and 40 ng/ml (70–100 nmol/L). Future investigations are needed to shed light on mechanisms for the beneficial effect of vitamin D on musculoskeletal health, on optimal timing and dosing for vitamin D supplementation, on the biological basis for sexual dimorphism in the response to vitamin D supplementation in the young, and on the key clinical outcomes, such as lifetime reduction in fracture risk. © 2006 Elsevier B.V. All rights reserved.

Keywords: Vitamin D; Bone mass; Lean mass; Bone geometry; Children; Adolescent; Trial; Optimal level

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1. General physiology of vitamin D

Antirachitic activity in cod-liver oil led to the concept that we now term, “vitamin”. The first vitamin was “antirachitic A” [1]. Through some quirks of science, the antirachitic molecule eventually became known as vitamin D. Since vitamin D is the structural material for a true hormone, it is, like cholesterol, a hormone precursor [2]. The classic role of vitamin D is to serve in the regulation of calcium and phosphate homeostasis, and through this it can affect bone mineralization and neuromuscular function [3,4]. Vitamin D is usually acquired via the skin when the B-ring of the cholesterol precursor, 7-dehydrocholesterol, is disrupted by exposure to ultraviolet light B. The resulting secosteroid isomerises spontaneously into cholecalciferol (vitamin D3). A molecule with vitamin D bioactivity can also be synthesized industrially from a plant steroid, ergosterol, producing ergocalciferol (vitamin D2). For many years, vitamin D2 was regarded as interchangeable with vitamin D3, and because of its lower cost, vitamin D2 was often used to fortify foods and for vitamin supplements. Clinical studies involving vitamin D now almost always involve vitamin D3.

Once it enters the circulation, vitamin D is either metabolized quickly to calcidiol [25(OH)D], whose concentration in serum or plasma is the accepted way to quantify of vitamin D nutritional status, or it distributes unmetabolized into muscle and adipose. 25(OH)D is a prehormone in the same sense that testosterone and T4 are, because like them, it is the circulating, immediate precursor of a signalling molecule. The kidney functions as a calcium-regulating gland that produces and secretes the hormone calcitriol [1,25(OH)2D] into the bloodstream to stimulate absorption of calcium from food. Many other tissues also possess the 25(OH)D-1-hydroxylase, but the 1,25(OH)2D they produce rarely reaches the circulation, but instead is for local regulation through vitamin D receptors (VDR) that respond to it [5].

The vitamin D hormone, 1,25(OH)2D regulates the transcription of bone matrix proteins and cell-cycle proteins, decreasing proliferation and enhancing differentiation of several cells such as enterocytes, keratinocytes, and osteoclast precursors [3].

Vitamin D binding protein (DBP) circulates at a concentration of over 4000 nmol/L, an extremely high concentration compared to all other steroid hormone transporters in plasma, with close to a 50-fold excess capacity for the normal total of all vitamin D metabolite concentrations [6]. For healthy people, vitamin D intake becomes toxic once the capacity of DBP is exceeded, resulting in increased unbound, or “free” calcitriol, which is common in toxicity despite an apparently normal total concentration of calcitriol [7].

It has long been a matter of debate, whether calcitriol, by acting on its steroid-like receptor, is the only mechanism by which molecules of the vitamin D system can elicit an effect. Traditionally, the vitamin D receptor (VDR; more correctly named, “calcitriol receptor”) is thought to mediate all functions of the vitamin D system. Unbound hormone crosses the plasma membrane, binds to the VDR, forms a hetero-dimer with the retinoid receptor, and the latter complex binds to vitamin D-responsive elements and transcription factors, thus enhancing the transcription of mRNAs [3,4]. The gene products increase calcium and phosphate absorption in the gut, induce calcium mobilization from bone, enhance calcium reabsorption in the distal tubules, and mediate various functions not related to calcium. While calcitriol is the only hormone known to stimulate intestinal calcium absorption, both parathyroid hormone (stimulated by low serum ionized calcium level) and calcitriol are required for enhancing calcium reabsorption in the kidney and inducing calcium mobilization from bone [4].
Calcitriol stimulates osteoblasts to produce receptor activator nuclear factor-kappa-B ligand (RANKL), which acts on its osteoclastic receptor causing bone resorption [4].

For years, calcitriol appeared to be central to everything related to vitamin D. Circulating 25(OH)D was regarded as an inactive precursor, and all but ignored in patients with chronic renal failure. However, the realization that many non-renal tissues possess 25(OH)D-1-hydroxylase has provided a mechanistic basis for clinical and epidemiologic findings that show 25(OH)D concentrations are normally more pertinent to health and disease prevention than are calcitriol concentrations [8]. Circulating 25(OH)D serves as the substrate for autocrine and paracrine control systems in many body tissues, and most of these are not related to calcium homeostasis [5]. Serum 25(OH)D – not only calcitriol – decreases parathyroid hormone secretion and parathyroid gland cellular proliferation [9], and evidently increases calcium absorption [10]. Consequently, maintenance of serum 25(OH)D concentrations and use of vitamin D supplementation to maintain values over 30 ng/mL (75 nmol/L) has recently become a fundamental part in the management of hyperparathyroidism in renal osteodystrophy [11].

The index disease for vitamin D is rickets in children and osteomalacia in adults [12]. These diseases occur at the most severely low concentrations of 25(OH)D — usually below 5–10 ng/ml (12.5–25 nmol/L). With long-term, milder deficiency, osteoporosis is regarded as the consequence of too little vitamin D [12]. As support for this, milder degrees of vitamin D inadequacy are associated with secondary hyperparathyroidism, increased bone turnover markers, and increased fracture risk [8,12]. To date, essentially all clinical research into vitamin D supplementation has focused on early childhood and the elderly. The consequences of marginal vitamin D nutritional status on musculoskeletal health in the skeleton of early adolescence – a critical time for bone mass accretion – are unclear; moreover, little is known about how to address the situation. This issue is of particular relevance because of the growing recognition that serum 25(OH)D concentrations are low in children and adolescents.

2. Hypovitaminosis D in children and adolescents

Increasing evidence supports a high prevalence of vitamin D insufficiency across age groups worldwide [13–18]. Risk factors for low serum 25(OH)D concentrations in “normal” subjects include temperate latitudes, season, duration of sun exposure, skin pigmentation, use of sun-block and clothing style. Groups at particular risk for hypovitaminosis D, due to decreased synthesis or increased requirements are the elderly, pregnant women, breast-fed infants, and adolescents. During adolescence bone mass increases substantially, a process that is largely determined by the genetic background of the individual, but that is also modulated by environmental factors. Vitamin D is essential for normal bone mineralization. Indirect and less abundant direct evidence support its role in bone mass accrual (see Sections 3 and 4); thus, the importance of defining the scope of the problem in children and adolescents worldwide.

As detailed in Table 1, there are large fluctuations in mean levels of 25(OH)D, in children and adolescents, between countries [19–37]. Levels range from the lowest of 5 ng/ml (13 nmol/L) in the winter in China to the highest of 57 ng/ml (142 nmol/L) in the summer in Norway (Table 1). The calculated non-weighted mean 25(OH)D level for the winter is 15.6 ng/ml (or 43 nmol/L) in 3584 subjects and the non-weighted mean for the summer is 28 ng/ml (or 70 nmol/L) in 2200 subjects (Table 1). Consistent predictors across studies for low vitamin D levels were female gender, lower socioeconomic status, and the winter season. In the largest
A population based study conducted in the US, the NHANES III study, based on a winter lower latitude subpopulation (November–March, median latitude 32°N), the mean 25(OH)D level in adolescent (ages 12–19 years) was 31 ng/ml (or 78.6 nmol/L) in 625 boys and 26 ng/ml (or 65 nmol/L) in 699 girls [15]. Based on a summer higher latitude (April–October, median latitude 39°N), the mean 25(OH)D level was 36 ng/ml (or 89.5 nmol/L) in 741 boys and 32 ng/ml (or 80.5 nmol/L) in 844 girls [15]. In the past, comparisons among isolated laboratories not taking part in such surveys suggested larger differences in results for 25(OH)D [38,39]. For laboratories that take part in the Vitamin D External Quality Assurance Survey (DEQAS) variations in 25(OH)D concentrations between methods have become minor, probably because laboratories adjust calibration or methods to ensure agreement of data with others [40].

### Table 1

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country/latitude</th>
<th>Age: mean/range</th>
<th>N/Gender</th>
<th>Season</th>
<th>25(OH)D nmol/L</th>
<th>25(OH)D ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aksnes, 1982</td>
<td>Norway/70°N</td>
<td>8–18 years</td>
<td>34 girls</td>
<td>Summer</td>
<td>142 (11)</td>
<td>57 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Winter</td>
<td>55 (10)</td>
<td>22 (4)</td>
</tr>
<tr>
<td>Taylor, 1984</td>
<td>USA, PENN/41°N</td>
<td>1.5–19 years</td>
<td>46 boys/girls</td>
<td>Summer</td>
<td>87 (20)</td>
<td>35 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>128 boys/girls</td>
<td>Winter</td>
<td>45 (14)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Oliveri, 1993</td>
<td>Argentina/55°S</td>
<td>8.5 years</td>
<td>42 boys/girls</td>
<td>Summer</td>
<td>46 (18)</td>
<td>18 (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Winter</td>
<td>25 (10)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Guillemant, 1995</td>
<td>France/49°N</td>
<td>13.5–15.75 years</td>
<td>28 boys</td>
<td>Summer</td>
<td>75 (18)</td>
<td>30 (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Winter</td>
<td>55 (16)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Docio, 1998</td>
<td>Spain/43°N</td>
<td>8 years</td>
<td>43 boys/girls</td>
<td>Summer</td>
<td>73 (24)</td>
<td>29 (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51 boys/girls</td>
<td>Winter</td>
<td>38 (13)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Kristinsson, 1998</td>
<td>Iceland/64°N</td>
<td>16 years</td>
<td>71 girls</td>
<td>Winter</td>
<td>41 (20)</td>
<td>16 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 girls</td>
<td>Winter</td>
<td>43 (22)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Guillemant, 1999</td>
<td>France/49°N</td>
<td>13–17 years</td>
<td>175 boys</td>
<td>Summer</td>
<td>59 (18)</td>
<td>24 (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Winter</td>
<td>21 (6)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Lehtonen-Veromaa, 1999</td>
<td>Finland/60°N</td>
<td>9–15 years</td>
<td>186 girls</td>
<td>Winter</td>
<td>34 (14)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>El-Hajj Fuleihan, 2001</td>
<td>Lebanon/33.5°N</td>
<td>10–17 years</td>
<td>169 boys/girls</td>
<td>Winter</td>
<td>42 (20)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Outila, 2001</td>
<td>Finland/60°N</td>
<td>14–16 years</td>
<td>178 girls</td>
<td>Winter</td>
<td>39 (14)</td>
<td>16 (6)</td>
</tr>
<tr>
<td>Du, 2001</td>
<td>China/40°N</td>
<td>12–14 years</td>
<td>1248 girls</td>
<td>Winter</td>
<td>13 (7.5)</td>
<td>5 (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Summer</td>
<td>27 (11)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Looker, 2002</td>
<td>NHANES USA/40°N</td>
<td>12–19 years</td>
<td>&gt;600 boys</td>
<td>(see text)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordon, 2004</td>
<td>Boston/43°N</td>
<td>11–18 years</td>
<td>307 boys/girls</td>
<td>Winter</td>
<td>50 (25)</td>
<td>20 (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Summer</td>
<td>65 (27)</td>
<td>26 (11)</td>
</tr>
<tr>
<td>Andersen, 2005</td>
<td>Europe</td>
<td>12.5 years</td>
<td>199 girls</td>
<td>Winter</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Sullivan, 2005</td>
<td>USA, Maine/44°N</td>
<td>9–11 years</td>
<td>3 girls</td>
<td>Winter</td>
<td>63 (18)</td>
<td>25 (7)</td>
</tr>
<tr>
<td>Marwaha, 2005</td>
<td>India/28°N</td>
<td>10–18 years</td>
<td>760 boys/girls</td>
<td>Overall</td>
<td>29 (18)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Lapatsanis, 2005</td>
<td>Greece/39°N</td>
<td>3–18 years</td>
<td>110 boys</td>
<td>Winter</td>
<td>43 (3)</td>
<td>17 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100 boys</td>
<td>Winter</td>
<td>67 (4)</td>
<td>27 (2)</td>
</tr>
<tr>
<td>Stein, 2006</td>
<td>South USA/34°N</td>
<td>4–8 years</td>
<td>168 girls</td>
<td>Winter</td>
<td>93 (28)</td>
<td>37 (11)</td>
</tr>
<tr>
<td>El-Hajj Fuleihan, 2006</td>
<td>Lebanon/33.5°N</td>
<td>10–17 years</td>
<td>179 girls</td>
<td>Winter</td>
<td>35 (19)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Viljakainen, 2006</td>
<td>Finland, Helsinki/60°N</td>
<td>11.5 years</td>
<td>228 girls</td>
<td>Winter</td>
<td>47 (17)</td>
<td>19 (7)</td>
</tr>
</tbody>
</table>
Vitamin D insufficiency encompasses a range with a varying upper limit depending on the study, due to lack of data unequivocally linking outcomes with insufficient vitamin D levels. This therefore partially explains the lack of an international consensus on an optimal vitamin D status for skeletal health [18]. Some indices used to indicate vitamin D repletion are serum parathyroid hormone (PTH) levels, 1,25(OH)₂D levels, bone density and fracture data. For the elderly, an expert panel recently suggested a minimal desirable ranging between 28 and 32 ng/ml (70–80 nmol/L) [18], whereas others suggest a lower cut-off of 20 ng/ml (50 nmol/L) as reflective of vitamin D repletion [41,42]. There are no similarly derived desirable levels for the younger age groups, primarily because of the lack of suitable clinical trial data. It can only be assumed that the health of children and adolescents is optimal at the same 25(OH)D concentrations as for other age groups. The elderly have increased demands due to decreased efficiency of intestinal absorption, and the young due to increased bone mass accrual. Many studies have demonstrated a very high prevalence of hypovitaminosis D in the youth. In several studies and especially in the winter, between 40% and 100% of children and adolescents fell short of the desirable level, even when set at the lower limit of 20 ng/ml (50 nmol/L, Table 1), especially in the winter (Table 1). This includes countries in Northern Europe [31], Finland [26], France [22,25], Spain [23], Greece [34], Lebanon [27,36], India [33], China [29], the northern US [30,32] and Argentina [21]. In the NHANES III study, 17% of adolescents in southern latitudes and 8% of teenagers from northern latitudes in the US fell below the more conservative cut-off of 15 ng/ml (37.5 nmol/L) [15]. If hypovitaminosis D is so prevalent, then what is the impact of low vitamin D levels on musculoskeletal health in the youth?

3. Impact of hypovitaminosis D on biochemical indices of calcium and bone metabolism

Lips recently reviewed possible criteria upon which to define appropriate vitamin D status, based on homeostatic pathways involved in normal vitamin D physiology [41]. Potential biochemical variables of interest would include changes in serum iPTH and calcitriol (1,25 (OH)₂D) concentrations, and bone turnover markers. The information can either be based on correlations between 25(OH)D and the above biological readouts of vitamin D status, as available in cross-sectional studies, or based on dynamic changes in PTH or calcitriol in response to vitamin D supplementation [41]. Desirable of 25(OH)D could be defined as those at which a further supplement in vitamin D does not increase serum 1,25(OH)₂D. Dietary intake of calcium [41], estrogen status (a modulator of intestinal calcium absorption at least in adults), and pubertal status (due to changes in calcitriol levels with puberty), are important covariates affecting the above listed biological readouts of vitamin D status. Therefore, our present overview will therefore specify calcium intake and age when detailing studies relating 25(OH)D to iPTH, calcitriol and bone remodeling, when such information is available.

3.1. Cross-sectional studies relating levels of serum 25 OH vitamin D to serum parathormone and calcitriol levels

The most commonly used approach to define an optimal vitamin D status is to study the relationship between circulating concentrations of 25(OH)D and iPTH [43]. A negative relationship between intact parathyroid hormone (iPTH) and 25(OH)D levels has been
described in children and adolescents, fitted to a linear or non-linear models depending on the study [22,25,27,30,33]. For ease of reading of this section 25(OH)D levels will be expressed as ng/ml and iPTH as pg/ml. To convert 25(OH)D from ng/ml to nmol/L multiply by 2.496, and to convert iPTH from pg/ml to pmol/L multiply by 0.105. Guillemant evaluated young normal male adolescents, on a mean calcium intake of 645 mg/day, and demonstrated a significant negative correlation of $-0.493$ between 25(OH)D and iPTH levels [22]. This observation was followed by a larger study with 394 observation points in male adolescents with a mean calcium intake of 805 mg/day [25]. The data described an inverse relationship, across a range of 25(OH)D concentrations between 4 and 48 ng/ml with iPTH concentrations ranging between 10 and 67 pg/ml. The data were fitted to a non linear model, and the authors suggested sharp increments in iPTH when 25(OH)D levels fell below 33 ng/ml [25]. El-Hajj Fuleihan et al. studied 346 Lebanese adolescent girls and boys recruited from schools, with a mean calcium intake of 700 mg/day. Serum iPTH levels ranged between 5 and 90 pg/ml and varied inversely with 25-OH vitamin D levels, which ranged between 3 and 45 ng/ml, $R = -0.36$ [27]. Gordon et al. reported results from 307 American adolescents recruited from a primary care clinic in Boston, with a calcium intake from milk of 500 mg/day, and described an inverse relationship between iPTH and 25(OH)D levels, $R = -0.29$, with 25(OH)D levels that varied between 7.5 and 73 ng/ml and iPTH levels between 10 and 165 pg/ml [30]. Marwaha also noted an inverse relation between 25(OH)D and iPTH in 760 Indian adolescents, with a calcium intake varying between 314 mg/day and 713 mg/day, $R = -0.202$ [33].

An examination of seasonal variations in the levels of 25(OH)D, and therefore iPTH and calcitriol levels, may give insight into the physiological relevance of decrements in 25(OH)D levels. In the study of Lebanese adolescents, the mean level for 25(OH)D was 22 ng/ml in the summer and 17 ng/ml in the winter, iPTH levels were 34 pg/ml and 32 pg/ml, in the two seasons respectively [27]. In the study from Boston, vitamin D levels decreased from 26 ng/ml in the summer to 20 ng/ml in the winter, and iPTH increased from 40 pg/ml to 50 pg/ml [30]. Guillemant demonstrated increments in 25(OH)D from 6.6 ng/ml in the winter to 30 ng in the summer, with inverse changes in iPTH from 30 to 23 pg/ml, but no changes in calcitriol levels [22]. Similarly, Oliveri evaluated 42 children with a mean age of 8 years, from the southernmost city in the world (latitude 55°S), and demonstrated seasonal changes in 25(OH)D levels, increasing from 9.8 ng/ml in the winter to 18.4 ng/ml in the summer, while iPTH levels decreased from 58.2 to 47.9 pg/ml, and again noted no changes in calcitriol levels [21]. Sullivan evaluated 22 adolescents girls from Maine and noted increments in mean 25(OH)D levels from 20 ng/ml in the winter to 30 ng/ml in the summer, with decrements in mean PTH levels from 29 pg/ml to 25 pg/ml [32]. Conversely, Lapatsanis documented no seasonal changes in either C-PTH nor $1,25(\text{OH})_2$ D levels in Greek adolescents, ages 11–18 years, when mean 25(OH)D levels decreased from a mean high of 27 ng/ml in the summer to a mean low of 13–21 ng/ml depending on the age group [34]. However, $24,25(\text{OH})_2$D levels changed in parallel with 25(OH)D, a finding that may be clinically relevant in view of the data suggesting a role for $24,25(\text{OH})_2$D in bone mineralization [44,45].

In summary, studies of adolescents involved mean calcium intakes between 300 and 1000 mg/day, and consistently showed an inverse relationship between 25(OH)D and PTH concentrations, with a correlation coefficient ranging between $-0.2$ and $-0.49$. The reports that provided individual data-points revealed a spread in 25(OH)D values between 3 and
73 ng/ml and in iPTH between 5 and 165 pg/ml [22,25,27,30]. The iPTH values above 70 pg/ml noted in the Boston study may be explained by the fact that almost half of the study subjects were African American, a group known to have higher PTH levels [30]. The studies on seasonal variations in calcitropic hormones reveal significant increments in iPTH levels when mean 25(OH)D decreased from the twenties and thirties to the low teens, in ng/ml [21,22,25,27,31]. No changes in calcitriol concentrations were noted [21,22], even in the study where 25(OH)D increased from a mean of 6 ng/ml to a mean of 30 ng/ml [22]. Changes in serum calcitriol levels in response to vitamin D replacement, as opposed to changes due to seasonal variations in 25(OH)D, are generally different (see Section 3.3 below).

It is currently unclear which increments in PTH levels are physiological and which are considered pathological [41]. One study suggests that reduced rates of skeletal remodeling during growth may result in increased bone density [46], and therefore by inference low vitamin D levels that raise PTH levels and therefore markers of bone remodeling would potentially be deleterious to bone health.

### 3.2. 25-Hydroxyvitamin D and markers of bone remodeling

There is ample evidence that bone resorption markers are higher in adults with vitamin D insufficiency [47] (the markers are after all among the criteria for defining a lack of vitamin D). In younger age groups, evidence for this is scarce and difficult to interpret due to the confounding effect of puberty on bone remodeling. In the study evaluating the prevalence of hypovitaminosis D in Lebanese adolescents, there were no correlations between 25(OH)D levels and the markers of bone remodeling, serum bony alkaline phosphatase, osteocalcin and C-telopeptide cross-links, in the overall study group with a mean age of 13 years, and a mean calcium intake of 642 mg in girls and 793 mg in boys [48]. However, in girls, serum levels of bony alkaline phosphatase and cross-laps were the highest in the subgroup with vitamin D insufficiency, 25(OH)D <20 ng/ml (<50 nmol/L) [48]. The relationship disappeared after adjusting for Tanner staging and gender [48]. In the Finnish vitamin D supplementation trial conducted in adolescent girls, mean calcium intake was 1200 mg/day, age 11(0.4) years, there were significant decrements in urinary deoxypyridinolines but not in urinary pyridinolines or serum osteocalcin in both groups treated with 200 or 400 IU/day of vitamin D, compared to placebo, in the per-protocol but not in the intent to treat analyses [37]. It is unclear whether the analyses were adjusted for pubertal status. Furthermore, the significance of the decrement in only one marker of bone remodeling is unclear, as it occurred in the absence of any change in serum iPTH levels, and in the light of very modest increments in 25(OH)D levels from 19 ng/ml (47 nmol/L) to 20 ng/ml (52 nmol/L) with the low dose and to 23.6 ng/ml (59 nmol/L) with the high dose vitamin D [37]. Conversely, Shou et al. conducted a randomized cross-over study in the winter in 20 Danish children, mean age 9.8 years, using 600 IU of D3 for 4 weeks [49]. While 25(OH)D increased from 13 to 19 ng/ml (33–47 nmol/L), there were no changes in either iPTH, 1,25(OH)₂D levels, osteocalcin or any of the markers of type I collagen turnover [49]. The negative findings in the latter study may be explained by the lack of adjustment for pubertal stages and the fact that the dose was inadequate in raising 25(OH)D levels to a more replete range.

In summary, the limited data available to-date does not provide convincing evidence for a relationship between 25(OH)D levels and bone turnover markers in the young.
3.3. Interventional studies evaluating impact of supplementation on 1,25(OH)₂ vitamin D and parathormone levels

A single dose of 150,000 IU of vitamin D₂ to 79 children, age 8.6(1.4) years maintained mean serum 25(OH)D levels at 17–18 ng/ml at 5 months, but failed to prevent the seasonal increment in PTH levels from 45.9 pg/ml to 51 pg/ml [50]. Guillemant administered three oral doses, 2 months apart, of 100,000 IU of vitamin D₃ starting September to 29 male adolescents and documented stable mean levels of 25 OH vitamin D of 20 ng/ml and no change in iPTH the following March, as opposed to decrements in 25(OH)D levels from 18.5 to 8 ng/ml and wintertime increment in iPTH from 28 to 40 pg/ml in the 28 untreated adolescents [51].

228 Finnish adolescent girls were randomized to placebo, 200 IU/day and 400 IU/day of vitamin D₃. The mean 25(OH)D increased from a baseline of 18 ng/ml by 2.5 ng/ml in the 200 IU group; and by 5 ng/ml in the 400 IU group, but there were no changes in iPTH concentrations [37]. Conversely, in a study of 191 Finnish adolescents given 400 IU of oral vitamin D₂ for 1 year failed to cause any changes in mean 25(OH)D level, which was at 13 ng/ml at study entry [52]. The lack of effect is partly explained by the fact that the investigators used vitamin D₂ which is now well known to be less than half as effective as vitamin D₃ at raising serum 25(OH)D concentration [53,54].

Supplementation of 21 mentally retarded children, ages 7–10 years, who had a baseline 25(OH)D of 21 ng/ml with 1600 IU/day of 25(OH)D orally for 7 days, induced a decrease in iPTH by 9 pg/ml and an increase in calcitriol by 20 pg/ml in children with a baseline 25(OH)D <10–12 ng/ml, solely an increase in calcitriol level by 12 pg/ml but no change in iPTH for those with an initial 25(OH)D between 12 and 20 ng/ml, and there was no change in either iPTH or calcitriol concentration for children with a baseline 25(OH)D >20 ng/ml [23]. These findings suggest that a desirable 25(OH)D concentration is one that exceeds 20 ng/ml (50 nmol/L) because at this point, PTH and calcitriol are stable and are minimally affected by vitamin D nutrition.

In a safety pilot study, our group treated groups of 16 healthy adolescents who, during summer, were given vitamin D₃ in doses equivalent to 2000 IU/day, but delivered once weekly (14,000 IU weekly) for 8 weeks [55]. The protocol raised mean 25(OH)D concentration from the initial 43±11 ng/mL – an exceptionally high concentration for children in Lebanon which we confirmed by retesting in two laboratories – and which was thus a good basis for tolerability to vitamin D, to a value after supplementation 54±19 ng/ml. For these, mean calcitriol levels did not change to a statistically significant degree. Calcitriol concentrations were 76±29 pg/ml at entry, and 89±26 pg/ml at termination [55]. In the larger clinical trial carried out subsequently to assess the effect of vitamin D supplementation on musculoskeletal parameters, 179 adolescent Lebanese girls were randomized to placebo, 200 IU/day and 2000 IU/day of vitamin D₃ given once weekly for 1 year. With 200 IU/day, there were no significant increments in either 25(OH)D or calcitriol concentrations. With the highest dose, 2000 IU/day, mean serum 25(OH)D concentration increased from 14±8 ng/ml to 38±31 ng/ml and 1,25(OH)₂D increased from 83±27 to 105±33 pg/ml at 1 year [36].

In summary, if 25(OH)D concentrations are <20 ng/mL (<50 nmol/L) there is an inverse relationship with iPTH, with suppression of iPTH with vitamin D supplementation. In contrast, if 25(OH)D exceed 33 ng/ml (83 nmo/L) suppression of PTH, or stimulation of
calcitriol does not occur to a meaningful degree. Although adolescence is unique because of the rate of bone accrual and endocrine changes, the patterns demonstrated here are consistent with PTH and calcitriol responses in adults [56,57].

4. Hypovitaminosis D and musculoskeletal health in children and adolescents

4.1. Descriptive observational studies relating 25(OH)D to bone density

Observational studies do not consistently reveal a positive relationship between serum 25(OH)D levels and bone mass. Stein et al. evaluated the relationship between 25(OH)D and bone mass in 168 pre-pubertal girls, mean age 6 years with a mean calcium intake of 823 mg, and a baseline 25(OH)D of 36 ng/ml. They noted a negative correlation between vitamin D and bone mass at the forearm ($R = -0.18$, $p = 0.02$), but not the spine or hip, that disappeared in the analyses adjusted for season, age, race, BMI, calcium intake and physical activity [35]. Two studies one conducted in 555 adolescent school children from India, and the other in 259 young girls from Iceland, did not show any relationship between 25(OH)D levels and bone density when measured at the forearm and calcaneus in the first study [33], and at the spine, hip and forearm in the second study [24]. The mean daily calcium intake was between 314 and 713 mg in the study from India, and 1500 mg in the study from Iceland, with mean 25(OH)D levels in the low-mid teens, in ng/ml, in both studies. Similarly, Outila et al. did not show any relation between 25(OH)D and radial bone density in 178 female Finnish adolescents with a mean calcium intake of 1216 mg/day [28]. However, the authors demonstrated that subjects with $25(OH)D < 16$ ng/ml had a radial BMD that was 1/4 of an SD lower than subjects who had a 25(OH)D above that cut-off [28].

El-Hajj Fuleihan et al. noted a positive correlation between baseline 25(OH)D levels, with a mean of 14 ng/ml, and baseline BMD at the spine, hip and radius, with correlation coefficients varying 0.16 and 0.24, depending on the skeletal site [36]. In a 3-year prospective study conducted in 171 Finnish girls with a mean calcium intake of 1500 mg/day, Lehtonen-Veroma noted that baseline 25(OH)D levels, with a mean of 15 ng/ml, correlated positively with accrual of areal BMD at the lumbar spine, but not the hip, $R = 0.35$, $p < 0.001$ [52].

All of the above analyses are limited by the confounding effect of environmental and anthropometric variables that have a powerful effect on bone mass, especially during growth. The convincing evidence for an impact of vitamin D on bone mass will therefore be provided by randomized vitamin D trials.

4.2. Randomized placebo controlled vitamin D trials

Two randomized trials have evaluated the effect of vitamin D on bone mass accrual in adolescents. 228 Finnish adolescent girls, age 11–12 years, were randomized in a double-blind trial to placebo, 200 IU, or 400 IU of vitamin D$_3$ (Scanpharm) given orally daily for 1 year [37,58]. At baseline their mean daily calcium intake was 1200 mg and mean 25(OH)D was 18 ng/ml. At 1 year the mean 25(OH)D decreased to 17 ng/ml in the placebo group, whereas it increased to 20.5 ng/ml in the 200 IU group, and to 23 ng/ml in the 400 IU group. The investigators first reported the results based on intent-to-treat analyses, and noted no differences in the changes in lumbar or femur BMD, BMC, or area, between the three groups
In a more detailed publication, the authors also noted no differences between the three treatment groups in changes in BMC in the analyses adjusted for changes in weight, in bone area, and in Tanner stages [37]. However, sub-group analyses based on compliant subjects, \(N=176\), revealed significant increments in femur BMC at the two doses compared to placebo and in increments in lumbar spine BMC at the high dose only [37]. The magnitude of the difference in BMC accrual between the three groups could not be evaluated because the mean values for the treatment groups considered in the compliance based analyses were not presented [37]. Sub-group analyses by pubertal stages, Tanner stages 1 and 2, versus stages 3 to 5, revealed no differences in BMC accrual between the two pubertal sub-groups at the femur, whereas BMC increments at the lumbar spine were reported as dose-dependent in mid-pubertal but not early pubertal girls [37]. Because of the narrow age group of the study subjects, 11–12 years, it is unclear how reliable the results based on the analyses by pubertal stages would be.

In the second trial, 362 Lebanese adolescent girls and boys, ages 10–17 years, were randomized in a double-blinded protocol to placebo, 200 IU or 2000 IU of vitamin D\(_3\) (Vigantol oil, Merck KgaA, Germany), given as once weekly for 1 year [36]. The mean daily calcium intake in girls was 676 mg and in boys 798 mg, and the entry 25(OH)D levels were 14 ng/ml and 16 ng/ml, respectively. Mean 25(OH)D levels increased to mid-high teens, in ng/ml, in the low dose group and into the high twenties to mid thirties, in ng/ml, in the high dose group, and calcitriol levels increased significantly in the high dose group in girls only [36]. There was no treatment effect on lean mass, BMD or BMC in either post-menarcheal girls or in boys (Table 2) [36,59]. In the overall group of girls, lean mass increased in both treatment groups \((p \leq 0.05)\), bone area and total hip BMC increased in the high-dose group \((p < 0.02, \text{Fig. 1})\). In pre-menarcheal girls, there was a significant increase in lean mass in both treatment groups, and consistent trends for increments in bone area, BMD and/or BMC at several skeletal sites. These changes reached significance at lumbar spine BMD in the low-dose group, and at the trochanter BMC in both treatment groups (Fig. 1) [36]. Because of the impact of treatment on both lean mass and bone area, adjusted analyses were conducted to assess the physiological pathway mediating the effect of vitamin D on bone mass accrual. The analyses suggested that the BMC increments were in large part explained by vitamin D induced changes in lean mass, to a lesser extent by vitamin D-induced changes in bone size, reflected by area [36]. In that trial the positive skeletal response to vitamin D replacement in girls contrasted with the lack of any positive response in boys. The sexual dimorphism in response to vitamin D supplementation may have several explanations. Boys had a higher calcium intake and exercised more than girls. There were gender differences in the severity of hypovitaminosis D at baseline, differences in the serum calcitriol levels achieved, and a lack of an increase in lean mass and bone area in boys, contrary to what was observed in girls. Furthermore, sex differences in the hormonal profiles achieved during puberty could explain the differences in the relationship between muscle and bone in boys and girls. To the authors’ knowledge, the trial in the Lebanese adolescents is the only one evaluating the impact of vitamin D replacement on musculoskeletal parameters in boys.

Because of the effect of vitamin D on lean mass and bone area in girls, both determinants of bone geometry, the investigators also evaluated the impact of vitamin D treatment on DXA-derived measures of bone geometry, using the hip structural analysis software [60]. The derived measures were cortical thickness, cross-sectional area, an index of resistance to
axial forces, and section modulus, an index of resistance to bending forces, at the narrow neck, trochanter and shaft. Vitamin D therapy resulted in positive changes in derived measures of cortical thickness, and in indices of resistance to axial forces and bending forces in proximal femurs of the overall group of girls and in pre-menarcheal girls [60]. The effect was in large part mediated by vitamin D-induced increments in lean mass [60]. Girls with the lowest 25(OH)D levels at study entry achieved the highest increments in bone mass and in parameters of bone geometry [36,60].

Limitations of the two trials include the use of DXA in a growing skeleton, a low power to detect differences in the efficacy between the two vitamin D doses, and a low power to evaluate the impact of pubertal status on the skeletal response to vitamin D, if any [36,37].

Table 2
Serum levels of vitamin D metabolites and percent change in BMC, lean mass, bone area and muscle strength at 1 year, in boys in different treatment groups and pubertal stages

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>200 IU/day</th>
<th>2000 IU/day</th>
<th>p-overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall:</td>
<td>S-25 (OH)D</td>
<td>17 (7)</td>
<td>20 (7)</td>
<td>35 (9)</td>
</tr>
<tr>
<td></td>
<td>S-1,25(OH)2D</td>
<td>78 (31)</td>
<td>88 (27)</td>
<td>90 (31)</td>
</tr>
<tr>
<td>LS BMC</td>
<td>14.0 (10.6)</td>
<td>15.2 (11.6)</td>
<td>12.5 (10.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>LS area</td>
<td>4.0 (7.2)</td>
<td>4.5 (7.6)</td>
<td>3.0 (8.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Total hip BMC</td>
<td>13.1 (9.5)</td>
<td>15.6 (10.4)</td>
<td>12.4 (8.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>Total Hip area</td>
<td>7.1 (6.5)</td>
<td>8.6 (6.4)</td>
<td>7.2 (5.5)</td>
<td>0.37</td>
</tr>
<tr>
<td>FN BMC</td>
<td>8.2 (7.2)</td>
<td>9.4 (8.8)</td>
<td>7.2 (8.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>FN area</td>
<td>3.7 (5.0)</td>
<td>5.0 (4.8)</td>
<td>3.8 (5.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Trochanter BMC</td>
<td>16.9 (17.5)</td>
<td>21.6 (17.6)</td>
<td>14.1 (16.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Trochanter area</td>
<td>10.3 (13.3)</td>
<td>13.9 (14.0)</td>
<td>9.8 (12.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Radius BMC</td>
<td>8.5 (5.3)</td>
<td>9.5 (7.2)</td>
<td>7.9 (5.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Radius area</td>
<td>4.4 (3.1)</td>
<td>5.2 (4.9)</td>
<td>4.7 (4.2)</td>
<td>0.58</td>
</tr>
<tr>
<td>Sub total body BMC</td>
<td>15.8 (8.4)</td>
<td>18.1 (9.2)</td>
<td>17.8 (31.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>Total body area</td>
<td>7.1 (5.4)</td>
<td>8.8 (4.8)</td>
<td>7.5 (4.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>Sub total body lean mass</td>
<td>13 (8)</td>
<td>16 (8)</td>
<td>12 (7)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Early-Puberty: (Tanner I–II)

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>200 IU/day</th>
<th>2000 IU/day</th>
<th>p-overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-25(OH)D</td>
<td>17 (6)</td>
<td>20 (5)</td>
<td>34 (6)</td>
<td>&lt;0.001*#</td>
</tr>
<tr>
<td>S-1,25(OH)2D</td>
<td>84 (35)</td>
<td>89 (31)</td>
<td>90 (31)</td>
<td>0.78</td>
</tr>
<tr>
<td>LS BMC</td>
<td>11.6 (9.9)</td>
<td>13.8 (12.6)</td>
<td>10.7 (9.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>LS area</td>
<td>1.5 (7.5)</td>
<td>3.3 (9.2)</td>
<td>0.4 (8.3)</td>
<td>0.40</td>
</tr>
<tr>
<td>Total hip BMC</td>
<td>16.3 (10.6)</td>
<td>17.1 (12.0)</td>
<td>13.4 (8.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>Total hip Area</td>
<td>10.6 (6.8)</td>
<td>10.8 (6.6)</td>
<td>9.1 (5.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>FN BMC</td>
<td>9.1 (7.0)</td>
<td>9.3 (10.8)</td>
<td>6.2 (7.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>FN area</td>
<td>4.7 (5.2)</td>
<td>6.2 (4.6)</td>
<td>3.8 (5.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Trochanter BMC</td>
<td>23.9 (19.8)</td>
<td>26.8 (19.4)</td>
<td>15.7 (14.2)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Trochanter area</td>
<td>16.0 (15.8)</td>
<td>18.7 (15.6)</td>
<td>12.8 (11.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Radius BMC</td>
<td>7.7 (3.7)</td>
<td>7.2 (7.7)</td>
<td>7.5 (4.7)</td>
<td>0.90</td>
</tr>
<tr>
<td>Radius area</td>
<td>4.4 (2.9)</td>
<td>5.0 (5.7)</td>
<td>5.3 (4.1)</td>
<td>0.73</td>
</tr>
<tr>
<td>Sub total body BMC</td>
<td>17.6 (7.0)</td>
<td>20.5 (9.0)</td>
<td>21 (5)</td>
<td>0.80</td>
</tr>
<tr>
<td>Total body area</td>
<td>8.9 (4.9)</td>
<td>11.0 (4.0)</td>
<td>9.0 (3.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Sub total body lean mass</td>
<td>16 (7)</td>
<td>19 (8)</td>
<td>13 (7)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

Values are means (SD).
Overall p-value and post hoc p values between subgroups by ANOVA.
#p<0.05 between PBO and high dose group by post-hoc ANOVA.
*p<0.05 between low and high dose by post-hoc ANOVA.
4.3. Vitamin D bone size (area) and height

Some studies evaluating the effect of calcium, or calcium enriched dairy products in the young reported increments in bone area or height in the growing skeleton [61–64], suggesting an effect of the intervention calcium on bone modeling [62]. An increased intake of protein and an increase in growth factors could explain the anabolic effect of the milk intervention on bone [62,64].

In the trial conducted in the Lebanese adolescents girls, in addition to increment in bone area most substantial at cortical sites, there was a trend was an increase in height in pre-menarcheal girls, the largest increments being at the high dose [36]. Such observation is reminiscent of the observation of the shorter stature in young adults from Ushuaia, a city...
where vitamin D deficiency is prevalent, as compared to adults from Buenos Aires, a city where UV radiation and winter vitamin D levels are more replete [65].

The increments in bone area at cortical sites, the trend for treatment difference in height, and increments in cortical thickness, in the Lebanese trial is consistent with an effect of vitamin D on modeling and bone growth [36,60]. This may be explained by a direct effect of vitamin D on periosteal apposition or indirectly through changes in lean mass/muscle mass, thus exerting an anabolic effect on long bones. Further studies are needed to investigate the possibilities raised by the above exploratory analyses. It will also be important to confirm that the higher bone density gained through vitamin D supplementation during adolescence remains higher into old age.

4.4. Safety of vitamin D in children and adolescents

The safety of vitamin D administration to the young is of particular interest because of the known increments in calcitriol with puberty [66,67] and because vitamin D supplementation at the equivalent dose of 2000 IU/day increased calcitriol levels in one study [36]. Circulating 25(OH)D can affect calcitriol concentrations through a number of mechanisms: The lack of 25(OH)D deprives 1-hydroxylase of substrate, hence, without 25(OH)D there can be no calcitriol production in vivo [68]. One determinant of a desirable 25(OH)D concentration is the establishment of a calcitriol concentration that is stable and no longer affected by higher 25(OH)D concentrations; therefore, the increase in calcitriol we observed with 14,000 IU/week of vitamin D can be taken as a sign that an optimal concentration has not been reached. Conversely, supplementation with 14,000 IU/week of adolescents of the same age group did not increase calcitriol further when baseline 25OHD levels were in the 40 ng/ml range [55]. In older adults, greater vitamin D supplementation than used here does not raise the serum calcitriol concentration [56,57]. In children, the effects of 25(OH)D on calcitriol may be different than in adults, because of differences in growth hormone and sex steroids, and their effects on 1-alpha-hydroxylase.

Administration of vitamin D as a once oral dose of 150,000 IU of D2 to 79 children with a mean age of 8.6 years stabilized 25(OH)D levels in the high teens, in ng/ml, but no changes in mean serum calcium or urinary Ca/Cr ration were noted at either 6 weeks or 5 months [21]. Similarly, administration of three oral doses of 100,000 IU of D3 every 2 months, in a case controlled study to male adolescents maintained serum 25(OH)D levels in the low twenties, ng/ml, 2 months after the last dose, no measurements of serum or urinary calcium were provided [51]. The safety of 2000 IU/day of oral vitamin D3, the upper limit for vitamin D intake, given as a weekly dose of 14,000 IU, was investigated in an 8 weeks placebo controlled study conducted in 24 adolescents [55]. Mean serum calcitriol levels increased from 42 pg/ml at entry to 53 pg/ml at 8 week, but no changes were noted in mean serum calcium or calcitriol levels [55]. These results were confirmed in a 1 year randomized placebo-controlled vitamin D supplementation trial, conducted in 340 adolescents, mean age 13 years, using the dose of 2000 IU D3 in one of the study arms [36,59].

In the entire study of 340 participants, 7 subjects (2%) had serum calcium levels above the upper limit of normal for children (10.7 mg/dl) at 1 year. The serum calcium values ranged from 10.8 to 11.1 mg/dl in these subjects, of whom 5 were in the placebo group and 1 each in the low-dose and high-dose vitamin D groups. Similarly, 5 subjects (1.5%) had
high serum 25(OH)D levels at the end of the study (63 ng/ml, 69 ng/ml, 103 ng/ml, 161 ng/ml, and 195 ng/ml): all were in the high-dose group, but none had concomitant hypercalcemia. Urinary calcium excretion was not measured in that study.

In summary, none of the studies using vitamin D₃ at doses as high as 2000 IU/day show any evidence for vitamin D intoxication, defined an elevated serum calcium in response to higher 25(OH)D concentrations [36,55].

5. Desirable levels of vitamin D and doses needed to reach such levels

Decrement in 25(OH)D levels from the twenties and thirties to the low teens, in ng/ml, result in increments iPPTH levels. Increments in 25(OH)D above 33 ng/ml (83 nmol/L) does not suppress PTH further [25]. Increments in 25(OH)D levels from the teens to the mid-thirties increased levels of 1,25 (OH)₂ D, but no changes occur when baseline 25(OH)D levels were in the forties, in ng/ml [36,55]. The biochemical data therefore suggests that 25(OH)D levels in the 30–40 ng/ml [75–100 nmol/L] range, may be desirable.

Desirable vitamin D levels should be also be defined by examining bone mass increments in response to vitamin D supplementation. In the study of the Finnish adolescents, with a mean calcium intake of 1200 mg/day, 200 IU and 400 IU of D₃ daily, raised 25(OH)D levels to 20.5 ng/ml (51 nmol/L) and 24 ng/ml (59 nmol/L), respectively, and increased bone mass [37]. The investigators could not rule out that higher levels may have achieved a more pronounced effect on BMC augmentation. In the study of the Lebanese adolescents, with a mean calcium intake of 675 mg/day, 200 IU and the 2000 IU of D₃ daily, raised 25(OH)D levels to 17 ng/ml (42 nmol/L) and 38 ng/ml (95 nmol/L), respectively, and bone mass increased at both doses [36]. Although there was a suggestion of a dose response, the study did not have the power to detect a significant difference in the response between the two doses. It is clear that vitamin D increasing 25(OH)D levels from the teens to the low twenties and mid thirties, in ng/ml, using doses of 2000 IU/day, increased BMC, BMD and may induce structural changes in bone [36,60]. The beneficial effect of lower doses of vitamin D (200 IU/day and 400 IU/day) on bone mass in the two trials may be due to local increments in calcitriol synthesis, since such doses mostly maintained and did not increase 25(OH)D levels above the 25 ng/ml (60 nmol/L) range [36,37].

This may lead one to conclude that safe and desirable 25(OH)D for children would be in the forties, in ng/ml, since they prevent increments in iPPTH levels, do not result in a further increments in the levels of calcitriol, and result in substantial increments in lean mass and bone mass. They also take into account the fact that the dietary calcium intake of adolescents worldwide is below that achieved by the adolescents in the Finnish study and below current recommendations [69].

It is reasonable to aim for 40 ng/ml (100 nmol/L) as the desirable target concentration for serum 25(OH)D in growing children. The dose of vitamin D₃ required to produce this concentration is difficult to define, because sun exposure is difficult to estimate for an entire population and the variability in baseline 25(OH)D levels (Table 1). In the winter, the non-weighted mean 25(OH)D level for adolescents from studies around the world is 15.6 ng/ml (39 nmol/L, Table 1).

We would suggest use of vitamin D supplements for children and adolescents who practice a culture of minimal exposure of skin surface to sunshine. In children, similarly to
adults, the mean 25(OH)D response to each microgram (40 IU) of additional oral vitamin D₃ is approximately 0.4 ng/mL (1 nmol/L) [36,37]. Therefore, based on the study, in which children initially averaged serum 25(OH)D concentrations below 20 ng/mL (<50 nmol/L), a vitamin D supplement dose of 2000 IU/day is a reasonable replacement approach for those with insufficient D levels and who avoid sunshine.

6. Conclusions and future directions

Hypovitaminosis D is widely prevalent in children and adolescents worldwide. Ample cross-sectional data documents inverse changes in iPTH levels as 25(OH)D levels decrease. Reports that associate low 25(OH)D levels with increased bone remodelling, or to decrements in bone mass are limited by the limited number of such studies in the literature and by their cross-sectional nature. Recently, two randomised clinical trials have been published that do support a beneficial effect of vitamin D replacement on bone mass in adolescent girls. In one of those trials, vitamin D supplementation increased lean body mass, bone area, and derived measures of bone strength. A model that incorporates the data presented here in is outlined in Fig. 2.

Although strides have been achieved over the last two decades in our understanding of the effects of hypovitaminosis D on musculoskeletal health in the elderly, many questions remain unanswered in the young. What is the physiological basis for the apparent sexual dimorphism in the response of musculoskeletal parameters to vitamin D replacement in adolescents? In which age group is vitamin D replacement the most beneficial? Are the increments achieved sustained into adulthood? How safe are high doses of vitamin D (>2000 IU/day) on genito-urinary system? What is the optimal 25(OH)D concentration and what dose should be recommended to ensure that level? What are the biological pathways for the beneficial effect of vitamin D on musculoskeletal parameters? Can changes in bone geometry and structure induced by vitamin D supplementation be confirmed? What are the best food vehicles to

Fig. 2. There is a direct positive effect of vitamin D increasing intestinal calcium absorption therefore enhancing bone mineral accretion, and an indirect effect suppressing secondary hyperparathyroidism, bone resorption, both of which will increase bone mass and structure. There is a positive effect of vitamin D on lean mass (muscle) thus increasing bone area and positively altering parameters of bone structure (geometry). The effect of vitamin D on bone structure may also be direct. The net result would be improved bone quality and increased bone mass.
fortify with vitamin D? What are the effects of too little vitamin D on non-classical health outcomes, such as autoimmune diseases in children? Implementation of multi-center, randomised trials including children of various age groups and stages of pubertal development, the use of improved assays to measure vitamin D metabolites, of peripheral QCT and measurements of body composition in the growing skeleton, will be instrumental to shed further light on the impact of hypovitaminosis D, the silent epidemic, on musculoskeletal health in children and adolescents.

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