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Invited Commentary

Seasonal variation in calcitropic hormones and bone accrual in puberty

The production of 25-hydroxycholecalciferol (25(OH)D) in the liver is dependent on vitamin D obtained from the diet and from exposure to UV light. UV rays stimulate the conversion of provitamin D in the skin to vitamin D, making it available to the liver for hydroxylation to 25(OH)D. The circulating concentrations of 25(OH)D are considered to be reflective of the individual's total vitamin D exposure (Holick, 1995*a*,*b*), yet there is no consensus on the concentration of serum 25(OH)D that would yield the most benefit for bone health (Chapuy *et al.* 1997; Thomas *et al.* 1998; Vieth, 1999). The definition for vitamin D deficiency based on serum 25(OH)D varies between studies, with the consensus setting the level at 25 nmol/l for adolescents (El-Hajj Fuleihan *et al.* 2001; Guillemant *et al.* 2001; Outila *et al.* 2001; Looker *et al.* 2002; Cheng *et al.* 2003). Suboptimal levels of vitamin D or 'insufficiency', as coined by many researchers, range from a base of 20–25 nmol/l to the upper limit of 40–50 nmmol/l or the point at which 25(OH)D suppresses parathyroid hormone (PTH) (Docio *et al.* 1998; Lehtonen-Veromaa *et al.* 1999; Du *et al.* 2001; El-Hajj Fuleihan *et al.* 2001; Guillemant *et al.* 2001; Looker *et al.* 2002; Gordon *et al.* 2004). However defined, the seasonal flux in 25(OH)D leading to increased prevalence of deficiency or insufficiency in the wintertime ranges from 3 to 75 % depending on the geographical location of the study and composition of the sample with regard to age range, ethnicity and sex (Lehtonen-Veromaa *et al.* 1999; El-Hajj Fuleihan *et al.* 2001; Guillemant *et al.* 2001; Looker *et al.* 2002; Andersen *et al.* 2005).

During puberty approximately 60 % of peak bone mass is accrued, leading scientists to surmise that seasonal flux in 25(OH)D may be detrimental to bone accrual and therefore peak bone mass. In this issue of the *British Journal of Nutrition*, Vilijakainen *et al.* (2006) provide cross-sectional data that document a lower serum 25(OH)D in winter and link it to lower bone formation and bone mineral density of the lumbar spine and total femur and higher PTH levels in early pubertal females. While the data appear to support the thesis that seasonal variation in 25(OH)D is detrimental to bone mass, we must consider: (1) the limitations in the current modalities to assess differences in bone metabolism over a 3–6-month period; (2) how different factors can confound the data.

The primary function of vitamin D during puberty is to increase the absorption of Ca to meet the mineral demands of the rapidly growing skeleton. Thus, insufficient 25(OH)D levels could dampen the intestine's ability to absorb Ca and thereby affect the availability of Ca for mineral deposition. While fractional absorption is related to the level of Ca consumed (Jackman *et al.* 1997), it has not been associated with 25(OH)D levels in children or adolescents who consumed greater than 800 mg/d (Abrams *et al.* 1995; Abrams, 1999). However, it is the absolute amount of Ca absorbed that determines if the adolescent is in positive Ca balance and therefore accruing bone mineral. In the study of Viljakainen *et al.* (2006), the participants surveyed in the wintertime consumed approximately 1400 mg Ca/d and this exceeds the recommended level of 900 mg for the Nordic Countries (NORD, 2004). Given a 34 % factor for absorption and a 5 % lower fractional absorption due to seasonal decline in 25(OH)D levels (Zittermann *et al.* 1998), the girls measured in the wintertime would have approximately 452 mg ca/d available for mineralisation, far above the estimated retention of 300 mg/d to meet the needs of mineralisation in early to mid puberty (Institute of Medicine & Food and Nutrition Board, 1997).

The negative relationship between PTH and 25(OH)D (Guillemant *et al.* 1995; El-Hajj Fuleihan *et al.* 2001; Outila *et al.* 2001; Cheng *et al.* 2003; Gordon *et al.* 2004; Viljakainen *et al.* 2006) has been the basis for proposing that seasonal flux in 25(OH)D has a negative effect on bone metabolism. PTH not only stimulates the conversion of 25(OH)D to 1,25-dihydroxycholecalciferol to increase intestinal absorption of Ca, it also stimulates bone resorption and increases the renal reabsorption of Ca to keep ionic Ca in tight control (Weaver *et al.* 1995; Abrams *et al.* 2000). A factor that may determine whether PTH levels are a detriment to bone mass in the growing skeleton is the level of Ca consumed (Bonofiglio *et al.* 2000; Iwamoto *et al.* 2004). PTH levels above the normal range are indicative of secondary hyperparathyroidism, readily treated by supplementation with vitamin D and Ca (Prince, 2003). If seasonal fluxes in 25(OH)D cause PTH to become elevated then the data of Viljakainen *et al.* (2006) should show a higher prevalence of abnormal PTH levels in wintertime compared with summer. A more likely explanation of their data is that relatively few participants had suboptimal Ca intake resulting in elevated PTH at all 25(OH)D levels below 70 nmol/l.

Difficulty in detecting seasonal fluxes in 25(OH)D on bone metabolism is confounded by how dietary Ca intake can affect the physiological processes involved in bone accrual and mineralisation during puberty. When collagen matrix is formed approximately 60 % of the osteocyte is mineralised within 2–3 months. The remaining mineralisation takes upward from 12–15 months and is referred to as secondary consolidation. It is estimated that secondary consolidation of the skeleton may take up to 3–6 years after longitudinal growth has ceased (Matkovic *et al.* 1994). During this extended time period, dietary Ca intake may modulate the net effect of seasonal flux of 25(OH)D on peak bone mass.

Ca supplementation studies support this concept (Rozen *et al.* 2003; Lloyd *et al.* 2004; Molgaard *et al.* 2004; Dodiuk-Gad *et al.* 2005). A cross-sectional study in early and mid puberty may provide data that support a negative effect of decline in 25(OH)D over wintertime (Viljakainen *et al.* 2006), but only longitudinal data over the entire pubertal period with seasonal estimation of 25(OH)D can support the net effect on peak bone mass.

Bone growth during puberty is represented by increases in bone size and mineral content with modest increases in bone mineral density (Bachrach *et al.* 1999). Dual-energy X-ray absorptiometry provides measures of bone area to represent bone size. If bone assessment techniques are made during or immediately after a rapid growth spurt there is an asynchrony of skeletal size and mineralisation (Bonjour *et al.* 1991; Fournier *et al.* 1997), resulting in what has been termed 'transient osteopenia'. Likewise, a seasonal decline in 25(OH)D levels accompanied by higher PTH levels could stimulate periosteal expansion and endosteal resorption, leading to a similar transient effect (Iwamoto *et al.* 2004). The study of Viljakainen *et al.* (2006) supports the idea that seasonal shifts in 25(OH)D lead to an increase in endosteal resorption as evidenced by a lower bone mineral density of the spine and femur with no difference in bone size. However, longitudinal studies are the gold standard that would document if seasonal decline in 25(OH)D results in a transient osteopenia or is a function of the selected cross-sectional study sample.

Biochemical markers of bone resorption and formation reflect the net activity of bone metabolism over the whole skeletal system, thus avoiding a varied response due to differential growth patterns of different skeletal sites when assessed by dual-energy X-ray absorptiometry (Bass *et al.* 1999). If seasonal variation in 25(OH)D levels increases endosteal resorption, elevated levels of urinary deoxypyridinoline, a marker of bone resorption, of about 17 % would be expected (Woitge *et al.* 2000). In contrast, the cross-sectional study of Viljakainen *et al.* (2006) only found decreases in osteocalcin, a marker of bone formation that has no seasonal variation (Woitge *et al.* 2000). During puberty bone formation exceeds bone resorption. However, the flux in markers over a 3–6-month period due to a decline in 25(OH)D has not provided consistent results during puberty (Zittermann *et al.* 1998; Lehtonen-Veromaa *et al.* 2002*b*). The net effect on bone formation and resorption may be difficult to detect due to high levels of Ca intake (Zittermann *et al.* 1998) or large variation in growth patterns of girls during puberty (Cheng *et al.* 2005). Cross-sectional comparison of groups measured in the summertime and wintertime are problematic due to large inter-assay variability in markers (8–10 %) (Schaller *et al.* 2005), stage of pubertal development (Zittermann *et al.* 1998; Ginty *et al.* 2004) and oestradiol levels (Zittermann *et al.* 2000).

In theory, seasonal variation in 25(OH)D could affect optimal accrual of peak bone mass. Research to date on seasonal variation in calcitropic hormones and bone mass measurements has produced many questions due to differences in study design, sexual maturity of the sample studied, level of serum 25(OH)D concentrations defined as deficient, and bone assessment modality. To understand the consequences of seasonal flux in 25(OH)D, we need to investigate how cortical and trabecular bone in children transitioning through puberty are affected by 25(OH)D levels at different levels of Ca intake. Blunting PTH by increases in vitamin D at moderate Ca intakes may compromise periosteal formation that leads to smaller bones, a risk factor for osteoporosis. On the other hand, vitamin D supplementation in low Ca consumers may increase fractional absorption of Ca while keeping PTH in the normal range (Guillemant *et al.* 2001; Lehtonen-Veromaa *et al.* 2002*a*). Although the study of Vilijakainen *et al.* (2006) provides data to suggest seasonal flux in 25(OH)D levels is detrimental to bone density in early and mid puberty, longitudinal studies are needed to confirm this cross-sectional association. The longitudinal study design should include seasonal estimates of 25(OH)D and PTH over the full course of puberty with annual bone assessments that include bone imaging techniques that are sensitive to changes in cortical and trabecular bone such as peripheral quantitative computed tomography (Cheng *et al.* 2003). In addition, a comprehensive evaluation of nutrient intake, oestradiol, biomarkers of bone formation during summer and wintertime and annual bone mass measurement techniques that can capture the impact on the whole body, spine, hip and radius are warranted.

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