

Predictors and Correlates of Vitamin D Status in Children and Adolescents with Osteogenesis Imperfecta

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Background: The prevalence of vitamin D deficiency and its consequences on bone in pediatric bone fragility disorders is not well characterized. In the present study, we evaluated determinants of vitamin D status in children and adolescents with osteogenesis imperfecta (OI) and assessed the relationship between 25-hydroxyvitamin D (25OH D) serum concentrations and lumbar spine areal bone mineral density (LS-aBMD).

Materials and Methods: This retrospective cross-sectional study comprised 315 patients with a diagnosis of OI type I, III, or IV (aged 1.1–17.9 yr; 161 girls) who had not received bisphosphonate treatment at the time of 25OH D analysis. In 282 patients (90%), LS-aBMD measurements were available at the same time.

Results: Serum concentrations of 25OH D ranged from 14 to 133 nmol/liter and were less than 50 nmol/liter in 86 patients (27%). Regression analysis revealed that age ($P < 0.001$), season ($P < 0.001$), and OI severity ($P = 0.048$), but not gender, were significant independent predictive factors of 25OH D levels. Serum 25OH D concentrations were negatively correlated with serum PTH levels ($P = 0.003$) and urinary cross-linked N-telopeptides of type I collagen to creatinine ratios ($P = 0.005$). Serum 25OH D levels were positively associated ($P = 0.02$) with LS-aBMD z-scores after accounting for OI severity, age, and gender.

Conclusion: Serum 25OH D levels are positively associated with LS-aBMD z-scores in children and adolescents with OI types I, III, and IV. (*J Clin Endocrinol Metab* 96: 3193–3198, 2011)

Vitamin D plays an essential role in calcium homeostasis and in the development and maintenance of the skeleton (1). Vitamin D stores can be assessed by measuring the serum concentration of serum 25-hydroxyvitamin D (25OH D), which is the most commonly used index of vitamin D status (2). Although vitamin D is an important determinant of bone health, there is no consensus as to which level of serum 25OH D should be considered optimal. Serum 25OH D levels between 50 and 80 nmol/liter are often recommended (3–5).

Although severe vitamin D deficiency can lead to rickets and osteomalacia, the effects of less severe vitamin D

deficits have not been fully established. In adults, mild vitamin D deficiency and consequent secondary hyperparathyroidism have been associated with increased rates of bone turnover, bone loss, and significantly higher osteoporotic fracture risk (6). In healthy children, however, randomized controlled trials have struggled to find an effect of vitamin D supplementation on bone density outcomes (7).

One might hypothesize that children and adolescents with bone fragility disorders are particularly sensitive to the additional challenge of vitamin D deficiency. However, data on this topic are very limited. One study on 85

children with various types of primary and secondary pediatric bone fragility disorders found a high prevalence of vitamin D deficiency, but clinical correlates could not be evaluated in any detail (8).

Osteogenesis imperfecta (OI) is the most frequent primary bone fragility disorder in children and adolescents (9). In a study on 71 children with OI, we found that 25OH D levels in the range from 13 to 103 nmol/liter did not correlate with histomorphometric parameters of bone mineralization or with bone mineral density (10). However, the study population may have been too small to detect an effect of vitamin D on bone mineral density. In the present study, we analyzed 25OH D levels and their determinants in 315 children with moderate to severe OI. We also evaluated the relationship between vitamin D status and bone mineral density.

Patients and Methods

Patients

This retrospective study comprised patients followed up at the Shriners Hospital for Children (Montréal, Québec). Inclusion criteria were a diagnosis of OI type I, III, or IV; the availability of 25OH D serum levels at the time of the first evaluation at the Shriners Hospital (so that results would not be influenced by the treatments received at this institution); and age 1–18 yr. Patients who had received bisphosphonate treatment before their first evaluation at the Shriners Hospital were excluded because bisphosphonates have a major influence on bone metabolism and bone density (11–13).

Three hundred fifteen patients (161 females and 154 males) were included in the study. The ages of these patients ranged from 1.1 to 17.9 yr. In 282 patients (90%), lumbar spine areal bone mineral density (LS-aBMD) measurements were available at the time of the 25OH D analyses.

Results of sequence analysis of *COL1A1* and *COL1A2*, the genes coding for collagen type I, were available in 254 patients and revealed disease-causing mutations in 222 patients. In the 32 patients in whom *COL1A1* and *COL1A2* sequence analyses were negative and in the 61 patients without DNA analysis, the diagnosis of OI was clinically asserted by the association of frequent fractures, low bone mass, and blue or gray sclera.

The patients' place of primary residence covered many countries (North and South America, Europe, North Africa, and the Middle East) and a wide range of climatic conditions, even though the majority of the patients were from Canada. The assessment of seasonal variability in 25OH D levels was restricted to this subgroup of patients residing in Canada ($n = 200$; 63% of the entire study population; living between latitude 45° and 55°). The study was approved by the Shriners Hospital Institutional Review Board and informed consent was obtained from legal guardians.

Anthropometric measurements

Height was measured using a Harpenden stadiometer (Holtain, Crymch, UK). Weight was determined using digital electronic scales for infants and mechanical scales for older children

and adults (Healthometer, Bridgeview, IL). Height and weight measurements were converted to age- and sex-specific z-scores on the basis of reference data published by the Centers for Disease Control and Prevention (14).

Biochemical measurements

Serum total calcium, phosphate, and alkaline phosphatase were measured using colorimetric methods (Monarch; Instrumentation Laboratories Inc., Lexington, MA). Serum active intact PTH (fragments 1–84) was determined by RIA (Diasorin, Stillwater, MN). Serum 25OH D was measured by RIA (Osteo SP; Incstar Corp., Stillwater, MN).

Urinary creatinine concentration (Cr) was determined colorimetrically. Urinary cross-linked N-telopeptides of type I collagen were quantified by ELISA (Osteomark; Ostex International Inc., Seattle, WA) using the second void sample of the morning. Results of urinary cross-linked N-telopeptides of type I collagen/creatinine ratios (uNTX/Cr) were expressed as a percentage of the mean value of age-specific reference data (15). Patients were fasting at the time of urine sampling.

Dual-energy x-ray absorptiometry

LS-aBMD was determined in the anterior-posterior direction at the lumbar spine (L1–L4) using a Hologic QDR 2000W or 4500 dual-energy x-ray absorptiometry device (Hologic Inc., Waltham, MA). Results were transformed to age-specific z-scores combining reference data from Salle *et al.* (16), Southard *et al.* (18), and Glastre *et al.* (17).

Statistical analyses

Raw results were transformed to age- and sex-specific z-scores from the average result in the reference population, using the published reference data cited in the description of each measurement technique. Variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean and SD.

Differences between two groups were tested for significance using the unpaired Student's *t* test or the Mann-Whitney *U* test, as appropriate. An ANOVA or the Kruskal-Wallis test was used to compare more than two groups, and Bonferroni's adjustment was used to adjust for multiple testing. Group differences in dichotomous variables were tested for significance using the χ^2 test.

To evaluate seasonal variability, serum 25OH D levels in samples collected during the months with the least sunlight in Canada (November to April) were compared with those collected during the months with the most sunlight (May to October).

Associations are given as Pearson correlation or Spearman rank correlation, as appropriate. Because the relationship between serum 25OH D levels and time of the year was not linear, a quadratic regression model, which best fits the data, was used.

Multiple regression analysis was used to assess potential predictors of serum 25OH D levels. Age, gender (coding: male, 1; female, 2), OI severity (coding: OI-I, 1; OI-IV, 2; OI-III, 3), and, in the subgroup of patients residing in Canada, season (November to April coded as 0; May to October coded as 1) were introduced as independent variables in models predicting serum 25OH D levels. The relationship between 25OH D levels and LS-aBMD z-scores was evaluated in a multiple regression model that included age, gender, OI severity, and serum 25OH D levels as predictors of LS-aBMD z-score. The effect of potential predictor variables was assessed in the stepwise mode.

TABLE 1. Clinical, biochemical, and bone densitometric results

Variable	n	All	n	OI type I	n	OI type III	n	OI type IV	P
Gender (male/female)	315	154/161	165	85/80	56	22/34	94	47/47	0.28
Age (yr)	315	7.2 (4.7)	165	7.3 (4.6)	56	6.6 (4.8)	94	7.5 (4.7)	0.48
Height (z-score)	313	−3.0 (3.2)	165	−1.0 (1.4) ^{a,b}	55	−7.6 (2.7) ^c	93	−3.9 (2.5)	<0.001
Weight (z-score)	309	−2.1 (2.8)	162	−0.6 (1.3) ^{a,b}	54	−5.6 (3.6) ^c	93	−2.5 (2.2)	<0.001
LS-aBMD (z-score)	282	−3.9 (1.6)	153	−3.0 (1.0) ^{a,b}	47	−5.4 (1.6)	82	−4.9 (1.4)	<0.001
Total calcium (mmol/liter) (normal: 2.25–2.63)	313	2.42 (0.12)	165	2.42 (0.11)	55	2.43 (0.17)	93	2.41 (0.11)	0.54
Phosphorus (mmol/liter) (normal: 1.23–1.62)	313	1.60 (0.21)	165	1.59 (0.21)	55	1.61 (0.25)	93	1.62 (0.20)	0.58
Alkaline phosphatase (IU/liter) (normal: <300)	314	287 (109)	165	301 (109)	55	272 (97)	94	273 (112)	0.08
uNTX/Cr (% reference mean)	233	117 (68)	112	109 (65)	41	127 (74)	80	124 (69)	0.21
PTH (pmol/liter) (normal: <10)	239	7.3 (2.7)	120	7.7 (2.9)	39	6.8 (2.7)	80	7.0 (2.2)	0.08
25OH D (nmol/liter)	315	64 (23)	165	65 (22)	56	65 (25)	94	61 (22)	0.36

Values are mean (sd). *P* values represent the significance of the difference between the three groups (ANOVA).

^a The results of *post hoc* analyses are significantly different between type I and type III OI groups.

^b The results of *post hoc* analyses are significantly different between type I and type IV OI groups.

^c The results of *post hoc* analyses are significantly different between type III and type IV OI groups.

All tests were two tailed, and throughout the study $P < 0.05$ was considered significant. These calculations were performed using the PASW Statistics software version 18.0 (SPSS Inc., Chicago, IL).

Results

Vitamin D status in patients with OI

Clinical and biochemical characteristics were similar between sexes, and therefore, results of girls and boys were analyzed as a single group (Table 1). As expected in an OI population, average height, weight, and LS-aBMD z-scores were very low overall and were higher in patients with OI type I than in OI types III and IV (19). There were no significant differences between OI types with regard to parameters of bone and mineral metabolism or serum 25OH D levels.

Individual serum 25OH D concentrations ranged from 14 to 133 nmol/liter and were negatively correlated with age (Fig. 1). Serum 25OH D concentrations were less than 15 nmol/liter in two patients (<1%), less than 25 nmol/liter in 10 patients (3%), less than 50 nmol/liter in 86 patients (27%), and less than 75 nmol/liter in 218 patients (69%).

Seasonal variation in serum 25OH D levels

Seasonal variation in serum 25OH D levels was studied in the subgroup of 200 patients residing in Canada. In this subgroup, the proportion of patients with serum 25OH D levels less than 50 nmol/liter was significantly higher in OI type III (nine of 21 patients; 43%) and OI type IV (22 of 49 patients; 45%) than in OI type I (29 of 130 patients;

22%) ($P = 0.005$, χ^2 test). Regression analysis revealed that serum 25OH D levels varied significantly with the time of the year in OI type I but not in the combined group of OI type III and IV patients (Fig. 2). In OI type I, average 25OH D serum levels varied by 71% from the seasonal trough (45 nmol/liter; reached in early January) to the seasonal peak (77 nmol/liter; reached in late July).

Multivariate stepwise regression analysis was performed in this group of patients to evaluate which putative determinants (age, gender, OI severity, season) were independently associated with 25OH D levels. This revealed that age ($P < 0.001$), season ($P < 0.001$), and OI severity ($P = 0.048$), but not gender, were significant independent predictive factors of 25OH D levels. In this model, the regression equation was: serum 25OH D level (nmol/liter) = $-1.5 \times \text{age (years)} + 11.6 \times \text{season} - 4.3 \times \text{OI severity} + 74.7$.

Relationships between 25OH D levels and bone parameters

In the whole study group, serum 25OH D concentrations were negatively correlated with serum PTH levels ($r = -0.19$; $P = 0.003$) and uNTX/Cr ($r = -0.19$; $P = 0.005$) but not with LS-aBMD z-scores ($P = 0.37$).

The level above which 25OH D concentrations should be considered sufficient is a matter of ongoing debate, but the current conservative consensus is that serum 25OH D levels should be at least 50 nmol/liter (3–5). Therefore, a value below 50 nmol/liter was used to define vitamin D deficiency. Compared with patients with deficient serum 25OH D concentrations, patients with serum 25OH D levels above 50 nmol/liter were younger [6.6 yr (sd 4.3) vs. 9.0 yr (sd 1.1); $P < 0.001$], had 10% lower serum PTH [7.1

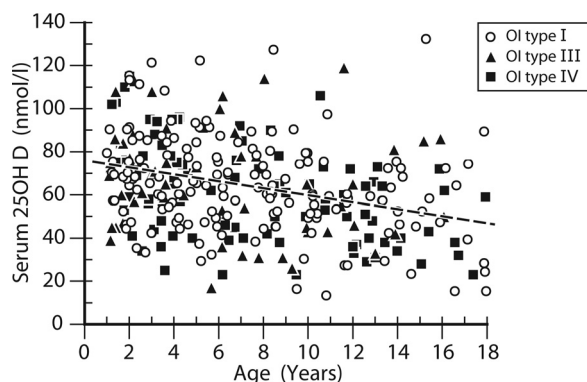


FIG. 1. Relationship between serum levels of 25OH D and age in the whole study group ($r = -0.33$; $P < 0.001$).

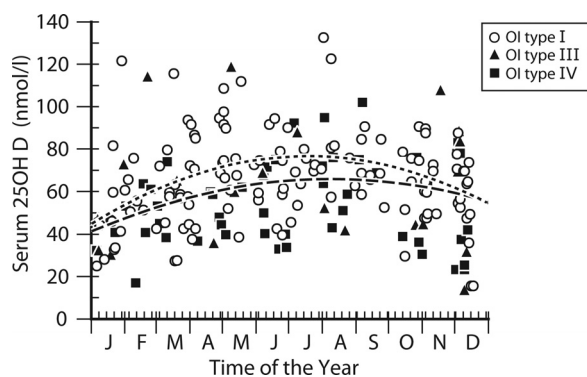


FIG. 2. Relationship between 25OH D serum levels and time of the year according to OI type in the Canadian subgroup. Serum 25OH D levels were significantly correlated with time of the year in OI type I ($r^2 = 0.16$; $P < 0.001$) but not in OI types III and IV ($r^2 = 0.05$; $P = 0.16$). The upper and lower parabolas represent graphs of quadratic function respectively for OI type I ($y = -0.0008x^2 + 0.32x + 44.8$) and OI type III and IV ($y = -0.0005x^2 + 0.22x + 41.2$), where x represents the day of the year and y the serum 25OH D levels.

pmol/liter (SD 3.4) vs. 7.9 pmol/liter (SD 2.3); $P = 0.03$) and 22% lower uNTX/Cr [110% of the reference mean (SD 91) vs. 134% of the reference mean (SD 55); $P = 0.02$] but similar LS-aBMD z-scores [-4.2 (SD 1.5) vs. -3.9 (SD 1.7); $P = 0.18$].

However, univariate analyses are probably not very sensitive to detect a relationship between 25OH D serum levels and LS-aBMD z-scores because LS-aBMD z-score varies widely and reflects the severity of OI. Therefore, multiple regression analysis was performed to evaluate whether 25OH D serum levels were independent predictors of LS-aBMD z-scores after accounting for OI severity, age, and gender. This revealed that all of these factors were independently associated with LS-aBMD z-scores ($P < 0.001$ for OI severity, $P = 0.001$ for age, $P = 0.02$ for serum 25OH D levels, and $P = 0.03$ for gender). The regression equation was: LS-aBMD z-score = $-1.3 \times$ OI severity + $0.058 \times$ age (years) + $0.008 \times$ serum 25OH D levels (nmol/liter) + $0.33 \times$ gender - 3.3. When serum PTH levels were added to this model, the correlation between serum 25OH D levels and LS-aBMD z-scores were

no longer significant, suggesting that the effect of 25OH D levels on LS-aBMD z-scores was mediated by PTH concentrations.

Discussion

In this study on children and adolescents with OI types I, III, and IV, we found that more than a quarter of the patients had serum concentrations of 25OH D below 50 nmol/liter. Serum levels of 25OH D decreased with age and varied significantly with season in patients with OI type I but not in patients with OI types III and IV. We found some evidence that lower serum 25OH D levels were associated with higher bone turnover and lower LS-aBMD z-scores.

Overall, 27% of our patients had deficient serum 25OH D concentrations. This proportion is similar to what was found in a recent report of children and adolescents with bone fragility (21%) (8) but is lower than in our previous study on OI patients (10). This difference in the prevalence of vitamin D deficiency between our studies is probably due to the fact that the present study population was on average younger and included a higher proportion of less severely affected patients than the previous report. Our observation that in this OI population serum 25OH D levels were lower in teenagers than in younger children mirrors the general situation in North American youths (1, 20).

Even though average 25OH D concentrations were similar between OI types, regression analyses revealed that more severely affected patients had lower 25OH D levels, once the effects of age, gender, and seasonal variation were accounted for. Whereas winter nadirs of 25OH D levels were similarly low in all OI types, patients with OI type I experienced a larger increase in 25OH D during summer than more severely affected patients. One might hypothesize that this was because patients with less severe bone fragility spend more time in the sun during summer than more severely affected patients who tend to have restricted mobility.

We note that in our patients 25OH D serum levels decreased less markedly during winter than what had been reported in previous studies on healthy youths. A French study had found average 25OH D serum levels as low as 20 nmol/liter during winter, whereas winter troughs of 33 nmol/liter were observed in a Finnish cohort (21, 22). This indicates that nutritional vitamin D intake was higher in our patients than in the healthy participants of these other studies. This might be due to a generally higher awareness of the importance of vitamin D in a cohort with a bone fragility disorder such as OI. Another potential explana-

tion is that vitamin D is added to milk in Canada but not in France and Finland, at least not at the time when those studies were performed. Indeed, when vitamin D fortification of milk was introduced in Finland in 2003, average 25OH D levels during winter increased by about 20% in young men aged 18–21 yr (23).

As previously described in healthy subjects, 25OH D levels in OI patients were inversely associated with PTH concentrations and markers of bone resorption, suggesting a possible deleterious effect of low 25OH D levels on bone (24). In accordance with this, we found that serum 25OH D levels were independently associated with LS-aBMD z-scores. This is a potentially important observation because it suggests that raising 25OH D levels could help to increase LS-aBMD z-scores in young OI patients. The regression equation in our study indicated that for every 1 nmol/liter increase in 25OH D levels, LS-aBMD z-score increased by 0.008. To put this into context, a controlled trial in healthy adolescents found that a daily vitamin D dose of 2000 international units led to 25OH D serum levels that were 26 nmol/liter higher than those achieved with a daily dose of 400 IU of vitamin D (25). If the same is true for OI patients, such a difference in 25OH D serum levels should translate into a LS-aBMD z-score difference of $26 \times 0.008 = 0.21$. In comparison, we have previously observed that bisphosphonate treatment increased LS-aBMD z-scores by about 1.0 in the first year of treatment (11, 26). Thus, the effects on LS-aBMD z-scores that could be achieved with higher vitamin D intake are probably relatively modest, but considering the generally good safety profile of vitamin D, additional supplementation might still be useful. Nevertheless, randomized controlled trials are required to assess whether vitamin D supplementation at higher than currently recommended doses are beneficial in children and adolescents with OI.

Conclusion

This cross-sectional study provides some evidence that serum 25OH D levels are associated with LS-aBMD z-score in children and adolescents with OI types I, III, and IV. Randomized controlled trials are warranted to assess whether LS-aBMD z-scores can be increased by higher vitamin D intake.

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