ORIGINAL ARTICLE

Vitamin D Levels in Children with Growing Pains

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ABSTRACT

Objective: To estimate the serum levels of vitamin D in children with growing pains and determine the relationship between serum vitamin D levels, parathormone and routine biochemical markers.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Paediatrics, Liaquat National Hospital, Karachi, from October 2008 to September 2009.

Methodology: Hundred children, aged 5-12 years presenting in Paediatric Outpatient Department of Liaquat National Hospital, Karachi, with limb pains, fulfilling the diagnostic criteria of growing pains, were included. Children with any systemic illness, organic cause of pain, rheumatologic disorders and signs of rickets were excluded from the study. Children were investigated for serum total calcium, inorganic phosphorus, alkaline phosphatase, vitamin D3 (25-hydroxecholecalciferol) and parathormone levels. On the basis of serum vitamin D3 level, patients were divided into 3 groups; group 1 with normal level of vitamin D3 (> 75 nmol/L), group 2 with vitamin D insufficiency (level between 50-75 nmol/L), and group 3 with vitamin D deficiency (level < 50 nmol/L). Significance of group proportions was determined using chi-square test with significance at $p < 0.05$.

Results: The mean age of the participants was 8.05 years with the majority (59%) being females. Only 6% had normal vitamin D levels. Over 95% of the children with vitamin D insufficiency had normal alkaline phosphatase and parathormone levels.

Conclusion: Hypovitaminosis D may have a role in pathogenesis of growing pains. All children with unexplained limb pains without identifiable organic pathology should be tested for vitamin D status, and treated, if necessary. Routine biochemical markers alone are not sufficient to detect all cases of hypovitaminosis D.

Key words: *Growing pains. Hypovitaminosis D. Unexplained limb pains.*

INTRODUCTION

Growing pains (GP), a well known clinical entity, is considered to be a normal occurrence in about 25% to 40% of children with no organic pathology.[1,2] GP has typical clinical characteristics; it is usually non-articular, located in the shins, calves, thighs or popliteal fossa, and is almost always bilateral. The pain usually occurs in the evening or at night with intensity varying from mild to very severe. The duration ranges from minutes to hours. Children feel better when they're held, massaged, and cuddled. It almost always resolves by morning. There are no objective signs of inflammation on physical examination.[1,3] Otherwise healthy children are most commonly affected by growing pains between the ages of 9 and 12, but they may also occur in younger age groups.[1]

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GP was first described in the medical nomenclature in 1823 by a French physician Marcel Duchmap.[4] After almost two centuries, it is still a poorly understood disease entity.[5,6] Few studies have been done to elucidate the etiology and pathogenesis of this common syndrome. It has been suggested that growing pains may be due to strain on muscles attached to growing bones. These muscles may tire easily and give pain.[1,7] Children with growing pains may have a low-pain threshold[8] and decreased bone strength.[9] Various psychological and familial factors may make the child more vulnerable to growing pains.[10] Theory of mechanical stress due to foot posture and flat feet with growing pains has recently been weakened.[11] Other factors like blood perfusion changes and joint hyper mobility were investigated but no conclusive results have been found.[7,12]

According to one study calcium intake in GP patients with lower bone strength group was found to be relatively low. It was postulated that a diet enriched in calcium and vitamin D might affect bone status and pain episodes,[9] but this theory has not been investigated.

The most important function of vitamin D is to maintain normal calcium homeostasis. Vitamin D increases the total intestinal absorption of calcium and phosphorus from 10-20% and 60% to 30-40% and 80%, respectively. In the setting of hypovitaminosis D, serum level of

calcium is first to fall, but phosphorus level is maintained within the normal range. This hypocalcaemia then leads to secondary hyperparathyroidism, resulting in an increased serum level of 1, 25 dihydroxycholecalciferol, normalization of serum calcium and a fall in plasma phosphorus level. This homeostasis is achieved by PTH-induced bone re-sorption, which also increases the serum level of alkaline pshosphatase. This condition, if left untreated, eventually leads to exhaustion of bone stores and recurrence of hypocalcaemia.[13]

There are no studies available highlighting the role of vitamin D deficiency in the pathogenesis of growing pains. The aim of this study was to estimate the serum levels of Vitamin D in children with growing pains and determine the relationship between serum vitamin D levels, parathormone and routine biochemical markers.

METHODOLOGY

This study was conducted at the Paediatric Outpatients Department of Liaquat National Hospital, Karachi, from October 2008 to September 2009. Hundred children aged 5-12 years, presenting with limb pains and fulfilling the diagnostic criteria of growing pains were enrolled for the study. Children with any systemic illness, organic cause of pain, rheumatologic disorders, obvious signs of rickets and malnutrition were excluded. Written consent was obtained from parents. A pre-designed questionnaire was filled by the doctor regarding demographic variables and milk intake. Serum concentrations of calcium (Ca), phosphorus (PO), alkaline pshosphatase (ALP), vitamin D3/25-hydroxycholecalciferol (25-OHD) and intact parathormone (PTH) were measured. Serum concentration of Ca was measured by O-cresolphtaleine complexone (Roche/Hitachi 912), PO by molybdate UV (Roche/Hitachi 912), ALP by IFCC method (Roche/Hitachi 912), 25-OHD by electrochemiluminescence immunoassay elecsys 2010 (Roche Diagnostic) and PTH by whole molecule double-antibody immunoassay (Nichols Advantage). All assays were performed according to manufacturer's instructions. Laboratory reference ranges included Ca at 2.3-2.75 mmol/L, PO 0.8-1.9 mmol/L in females and 0.97-1.94 mmol/L in males; ALP < 269 U/L (4-6 years) and < 300 U/L (7-12 years) vitamin D i.e. 25-OHD was taken at normal > 75 nmol/L, insufficiency at 50-75 nmol/L and deficiency at < 50 nmol/L. PTH reference range was set according to age and gender. At 5-6 years it was taken as 1-13 ng/L in female and 4.4-16 ng/L in male. At 7-8 years it was 2-0.7- 25 ng/L for girls and 2.5-27 ng/L for boys; at 9-10 years it was 2-30 ng/L and 4.6-34 ng/L for girls and boys respectively and at 11-12 years it was 4.3-34 ng/dL for girls and 2.5-25 ng/dL for boys.

Serum levels falling out of the reference ranges were considered abnormal (high or low). Patients were divided into 3 groups according to serum 25-OHD level: group 1 with normal levels, group 2 with insufficiency and group 3 with vitamin D3 deficiency.

Data was analyzed using SPSS version 13. Quantitative variables were reported as mean and SD while qualitative variables were described in proportions. Association between serum 25-OHD and calcium, ALP, PTH was evaluated using chi-square test and p-value calculated. A p-value ≤ 0.05 was taken as statistically significant.

RESULTS

A total of 100 patients were studied. Mean age of the study population was 8.05 ± 2.28 years (range 5-12 years). The study group comprised of 41% males and 59% females. Mean milk intake was 0.34 ± 0.11 L/day; 17% of the study population was using vitamin D fortified milk. Mean values with range and standard deviation for serum calcium, phosphorus, ALP, 25-OHD and PTH are given in Table I.

Hypocalcemia was found to be more common in patients with vitamin D deficiency (26%) as compared to those with vitamin D insufficiency (22.7%) but this was not found to be statistically significant (p=0.863, Table II).

ALP was elevated in 38 patients (38%) out of whom 37 (97.3%) had vitamin D deficiency while one (2.7%) had vitamin D insufficiency. Sixty two (62%) of the patients had normal serum level of ALP (p < 0.001, Table III).

Table I: Biochemical characteristics of the 100 participants.

Biochemical parameter	Value		Frequency (percentage)	
	Mean ± SD	Range		
Serum calcium, mmol/L	2.4 ± 0.145	1.98 - 2.75	Normal	74 (74%)
			Low	26 (26%)
Serum phosphorus, mmol/L	1.34 ± 0.27	0.87 - 1.9	Normal	96 (96%)
			Low	4 (4%)
Serum ALP, U/L	309.06 ±165.63	125 - 1020	Normal	62 (62%)
			High	38 (38%)
Serum 25- hydroxycholecalciferol (Vit D3), nmol/L	40 ± 21	7.5 - 117	Normal	6 (6%)
			Insufficiency	22 (22%)
			Deficiency	72 (72%)
Serum PTH, ng/L	27.02 ± 24.86	5 - 137	Normal	66 (66%)
			High	34 (34%)

Mean value of serum PTH level was 27.02 ng/L with a SD of 24.86 and range of 5-137. Secondary hyperparathyroidism was found in 34% (n=34) patients (p=0.002). Thirty two patients (44.44%) with vitamin D deficiency (n=72) had associated secondary hyperparathyroidism. While one out of 22 patients (4.44%) with vitamin D insufficiency had elevated PTH level (Table III).

Table II: Comparison between serum calcium/phosphorous and vitamin D3 levels (n=100).

Serum vitamin D3	Serum calcium		p-value
	Low	Normal	
	n (%)	n (%)	
Normal	2 (33.33%)	4 (66.67%)	
Insufficiency	5 (22.77%)	17 (77.23 %)	0.863
Deficiency	19 (26.38%)	53 (73.61%)	

Serum vitamin D3	Serum phosphorus		p-value
	Low	Normal	
	n (%)	n (%)	
Normal	1 (16.67%)	5 (83.33%)	
Insufficiency	0 (0%)	22 (100%)	0.18
Deficiency	3 (4.17%)	69 (95.83%)	

Chi-square test at 0.05 level of significance.

Table III: Comparison between serum vitamin D, alkaline phosphatase and parathormone levels (n=100).

Serum vitamin D	Serum alkaline phosphatse		p-value
	High	Normal	
	n (%)	n (%)	
Normal	0 (0%)	6 (100%)	
Insufficiency	1 (4.55%)	21 (95.45%)	< 0.001
Deficiency	37 (51.39%)	35 (48.61%)	

Serum vitamin D	Serum parathormone		p-value
	High	Normal	
	n (%)	n (%)	
Normal	1 (16.67%)	5 (83.33%)	
Insufficiency	1 (4.55%)	21 (95.45%)	0.002
Deficiency	32 (44.44%)	40 (55.56%)	

Chi-square test at 0.05 level of significance.

DISCUSSION

Non-specific musculoskeletal pain has been widely linked to hypovitaminosis D in otherwise healthy adults and elderly.[14,15] Growing pains could be a specific manifestation of vitamin D deficiency in children.

It was found that 94% of the children with growing pains had hypovitaminosis D, 72% of them being deficient. Dietary intake of calcium, in the form of milk and other dairy products, was found to be low in the study population. Only 17% of the children were using vitamin D fortified milk. It suggests that there could be a relationship between growing pains and hypovitaminosis D. Several decades ago, growing pains were said to be a manifestation of calcium deficiency by Abraham Jacobi. He also suggested an etiological similarity between growing pains and nocturnal cramps in adults due to calcium deficiency.[16] Recently, growing pains have been linked to vitamin D and calcium deficiency by other authorities as well.[17,18] James Dowd, in a blog on vitamin D, said that growing pains are nothing else but a clinical expression of hypovitaminosis D.[17]

In this study population, only 26% of the total patients had hypocalcaemia (all had vitamin D deficiency). This is in contrast to the observations which reported low serum Ca in 46% of patients with hypovitaminosis D.[19] This contrast was seen because their study sample comprised of patients with musculoskeletal symptoms referred to them with abnormal routine biochemistry.

Ninety seven percent of the children had normal serum PO levels which was almost similar to normal serum PO in 81% of patients reported by Peacey.[19]

Although 51.39% of our patients with vitamin D deficiency had elevated serum ALP level, however, vitamin D insufficiency was not found to be related to raised ALP level. These results are in accordance with results of a study from Tehran which highlight the poor sensitivity of usual biochemical parameters (Ca, PO, ALP) to detect vitamin D insuffiency. Sensitivity of at least one biochemical variable to detect severe, moderate and mild vitamin D deficiency was 24.2%, 13.8%, and 6% respectively.[20] Other authors have also reported routine biochemical markers of bone turnover to be unreliable even in the setting of secondary hyperparathyroidism.[21]

Bone turnover markers, generally advised by the physicians include serum calcium, PO and ALP and are considered to be reflective of the bone homeostasis. However, in this study, only a minority of patients were found to have hypocalcaemia (6%), hypophosphatemia (3%). ALP level was elevated in 38% of patients.

An inverse relationship between PTH and 25-OHD levels was also found in patients with vitamin D deficiency, 44.44% of patients with vitamin D deficiency had secondary hyperparathyroidism. A significant rise in PTH has been reported with low serum 25-OHD levels by other authors as well. However, the study also concludes that hypovitaminosis D may co-exist with a blunted PTH response.[22]

Estimation of serum levels of 25-OHD and PTH is not only expensive but also not widely available. In an economically stripped population, like ours, these tests are not done in routine. In an earlier study done in children with limb pains from Kashmir, serum ALP concentration, only, was used as an indicator of the bone status.[23] The study provides information that serum levels of ordinary bone turnover markers may be normal in patients with hypovitaminosis D and these alone, in the absence of serum levels of 25-OHD and

PTH, are not true indicators of bone status. Routine biochemical markers if used alone are likely to miss a majority of patients with hypovitaminosis D.

Low serum concentrations of 25-OHD with secondary hyperparathyroidism leads to decreased bone mineral density and resultant osteopenia. It is well known that individuals with low bone mass density in childhood and around adolescence have a higher risk of sustaining osteopenic fractures later in life.[24,25] Further studies are required to determine if children with growing pain who have hypovitaminosis D are more likely to have low bone mineral density and greater likelihood of fractures in later life.

CONCLUSION

There was a significantly high frequency of hypovitaminosis D in children with growing pains. Growing pains could be an early manifestation of underlying histological changes in bone matrix when routine biochemical markers are not markedly altered. This suggests need to optimize children's vitamin D intake. Serum concentration of ALP, generally used by physicians for screening, is not a true indicator of bone status in the setting of hypovitaminosis D and it is only raised when patients have vitamin D deficiency.

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