A Prospective Study for Causal Relationship of Growing Pains and Vitamin D

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ABSTRACT

Introduction: Growing pains is a common clinical entity. It is a frequent cause of outpatient visits in paediatrics. Despite being a common problem, little is known about its aetiology. Recent studies have shown some relief in growing pains with Vitamin D therapy. The aim of this study was to find a causal relationship between growing pains and Vitamin D.

Material and methods: 92 patients aged between 5 and 12 years were included in study. Vitamin D levels and pain severity using wong baker faces pain scale were measured at first contact with patient and repeated at 3 months after giving Vitamin D.

Results: Results before and after giving Vitamin D were compared by statistical analysis using excel and SPSS. An improvement of pain score from mean of 7.4 to mean of 1.4 (P value<0.001) was noted.

Conclusion: Vitamin D therapy improved quality of life by resolving pain. However further studies are needed to establish a definite causal relationship between growing pains and vitamin D using Randomized control trails.

Keywords: Vitamin D, Growing Pains, Adolescents, Leg Pains, Calcium, Phosphorous

INTRODUCTION

Growing pains (GP) is a well-known clinical entity. The estimated prevalence of growing pains worldwide ranges from 3 to 37%.[1,2] GP is familial and mainly effects children aged 4–12 years, and are most prevalent in those aged 4–6 years.[3] 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 severe. The duration ranges from minutes to hours.[1] It almost always resolves by morning. There are no objective signs of inflammation on physical examination.[2] Otherwise healthy children are most commonly affected by GP.[4] Most paediatricians and general practitioners in their day-to-day clinical practice often come across children complaining of pain in their legs. These pains may sometimes point to serious underlying conditions such as malignancies, infections or injuries. However, majority of the cases may be due to 'growing pains (GP)' that have a benign and self-limiting course.[5] GP though considered benign, can cause considerable anxiety in the parents. Sometimes, the child wakes up in the middle of night with extreme agony, complaining of severe pain in the legs. There are no symptoms in the morning and paediatrician finds no abnormality on physical examination. Many aetiologies have been suggested for Growing pains but even after about two centuries of its first appearance in literature, the exact cause of GP still remains to be found. Recently many authors started studying role of calcium and vitamin D in the pathogenesis of GP. With this background we started to study whether Vitamin D and calcium have a role in GP and are there any other epidemiological determinants of GP?

Vitamin D is a group of fat-soluble pro hormones which were identified after the discovery of the anti-rachitic effect of cod liver oil in the early part of the 20th century.[6] The two major biologically inert precursors of vitamin D are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol).[7] Vitamin D3 is formed when 7-dehydrocholesterol in the skin is exposed to solar ultraviolet B (UVB, 290-320 nm), and is then converted to pre-vitamin D3 in a heat-dependent process, pre-vitamin D3 is immediately converted to vitamin D.[8] Excess UVB rays transform pre-vitamin D3 into biologically inactive metabolites, tachysterol and lumisterol. Vitamin D2 is plant derived, produced exogenously by irradiation of ergosterol, and enters the circulation through diet. Both vitamin D precursors resulting from exposure to the sunshine and the diet are converted to 25-hydroxyvitamin D [25(OH)D] (calcidiol) when they enter the liver.[9] 25(OH) D is the major circulating form of vitamin D and is used to determine vitamin D status. In order to be biologically active, additional hydroxylation in the kidneys is needed to form active 1, 25-dihydroxyvitamin D [1, 25(OH) 2 D] (calcitriol). Humans obtain vitamin D through dietary intake and exposure to sunlight. Very few foods naturally contain vitamin D. Oily fish such as salmon, mackerel, and sardines are rich in vitamin D3.[10] Egg yolks are reported to contain vitamin D though the amounts are highly variable.[11]

Vitamin D plays an important role in maintaining an adequate level of serum calcium and phosphorus.[12] Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed.[13] The most important function of vitamin D is to maintain normal calcium homeostasis. Vitamin D increases the total intestinal absorption of calcium

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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 phosphatase. This condition, if left untreated, eventually leads to exhaustion of bone stores and recurrence of hypocalcaemia.[14]
An association between the vitamin D level and chronic pain conditions has been described in adults; the patient's pain condition improved with vitamin D supplementation.[15,16]
Vitamin D deficiency occurs when people do not have an appropriate dietary intake or exposure to UVB rays. It is universally accepted that the circulating level of 25-hydroxyvitamin D should be used as an indicator of vitamin D status due to its ease of measurement, long half-life in circulation (approximately 2 or 3 weeks). Many factors decrease conversion of 7- dehydro cholesterol to vitamin D-3 like increased melanin in dark skinned people, measures to decrease sun exposure like sunscreens, children spending less time outside. Vitamin D insufficiency is defined as a 25(OH) vitamin D serum concentration of <20 ng/ml (25–50nmol/l). Whereas a level of ≥ 20 ng/ml is considered sufficient/optimal.[17,18]
Wong Baker Faces Pain Rating Scale[19] was developed by Dr. Donna Wong & Connie Morain Baker in 1988 for use in children 2 years and older. Face of the child is compared with the visual scale. Child and his parents are first explained about the use of the scale and then asked to choose the face which describes his/her pain and the score is then assigned accordingly.

MATERIAL AND METHODS

The study was a prospective observational study, 92 patients of either sex, age range being 5 to 12 years who presented to our outpatient department with complaints of GP were enrolled as defined by inclusion and exclusion criteria
All patients in age group of 5 to 12 years who present to our outpatient department with Growing Pains (GP) which is defined as a pain which is intermittent, bilateral in distribution, more during afternoon and evening hours, affects mainly thighs and calf muscles. Physical examination is normal and markers of inflammation are negative. Any child who had a systemic illness, rheumatologic disorder, local swelling, erythema, tenderness, a history of recent trauma or on multivitamin supplements was excluded.
A written consent was taken from all enrolled subjects. All subjects were evaluated as per pre-defined format which included history of pain and its characteristics; height and weight were measured using a standard stadiometer and a digital scale. The body mass index (BMI) was then calculated for all subjects. Initially, all of them underwent evaluation of a complete blood count, the erythrocyte sedimentation rate (ESR) and levels of serum total calcium, serum phosphate, alkaline phosphatase (ALP) and C-reactive protein.
Pain severity was evaluated using Wong-Baker Faces Pain Rating Scale. A pain score<4 is considered mild, score of 4-6 is considered moderate and a score > 6 is severe. The use of this scale takes usually less than a minute.
The serum 25 (OH) D levels was measured using an chemiluminescence enzyme immunoassay method in the department of Immunology and Molecular Medicine SKIMS Soura Srinagar. Vitamin D insufficiency was defined as a level of <20ng/ ml whereas a level ≥20 ng/ml was considered sufficient. Based on vitamin D levels patient were divided in two groups.

Group 1 consisted of patients who had vitamin D insufficiency (a level < 20 ng/ml).[17,18]

Group 2 consisted of patients who had normal vitamin D levels (a level of ≥ 20 ng/ml).[17,18]

Patients who had vitamin D insufficiency were given vitamin D 60,000 IU weekly 5 doses (total 3 lac units) and oral calcium 1000mg/day for one month.
After 1 month of vitamin D treatment, the children in group 1 underwent measurement of serum vitamin D, calcium, and urinary calcium / creatinine levels in order to check if the vitamin D dose had been effective and to monitor side effects such as hypercalcemia.
Pain Score (baseline and at three months) and vitamin D levels (baseline and at one month) in **group 1** patients was compared.
Statistical Analysis was done using SPSS (Statistical Package for the Social Sciences) version 20. Normality of data was evaluated using Shapiro-Wilk Test and by finding skewness and kurtosis of the data. Continuous data with normal distribution was analyzed by paired T– test and represented by mean and standard deviation (SD). Continuous data with skewed distribution was checked by Wilcoxon sum test and represented by median and Interquartile Range. Properties were analyzed by Chi- Square / Fischer's test and represented as percentage. Logistic regression model was done to assess relation of various variables (age, sex, weight, BMI, serum phosphate, alkaline Phosphate, vitamin D levels) with the severity of pain.

RESULTS

Table 1: Demographics of study subjects
Table 2: Biochemical parameters comparison in study subjects.
Table 3: comparison of pain score and vitamin D levels before and after treatment in group 1 subjects
Table 4: LOGISTIC REGRESSION MODEL FOR PAIN SCORE > 6

DISCUSSION

There are a very few studies which have studied the relationship of GP with vitamin D. We hypothesized that vitamin D has a causal relationship with GP and for pain measurement we used wong baker faces pain scale.[19] In this scale the face of the child is compared with the visual scale.

	All subjects	Group1	Group2	P value
Number of subjects	92	80	12	
Age(mean± SD)	7.52±2.12	7.53±2.23	7.42±1.24	0.85
Sex(male+ female)	56+36	49+31	7+5	1.00
Height percentiles (mean± SD)	44.71±15.77	45.04±16.80	42.50±4.91	0.61
Weight percentiles (mean± SD)	41.49±16.33	40.54±16.99	47.83±9.11	0.15
BMI (mean± SD)	15.75±2.83	15.58±2.93	16.83±1.84	0.16

Table-1: Demographics of study subjects

	All subjects	Group1	Group2	P value
Serum calcium	8.84±0.65	8.74±0.57	9.5±0.79	<0.001
Serum phosphate	4.35± 0.37	4.34± 0.38	4.42± 0.29	0.51
Alkaline phosphatase	111.00± 33.78	112.23± 32.95	107.08± 40.21	0.63

Table-2: Biochemical parameters comparison in study subjects.

	Before treatment	After treatment	P value
Vitamin D levels	10.08±3.24	34.6±6.16	< 0.001
Pain score	7.70± 1.31	1.40± 0.97	<0.001

Table-3: Comparison of pain score and vitamin D levels before and after treatment in group 1 subjects

	Unadjusted			Adjusted		
Variable	O.R	95% C.I.	P. value	O.R	95% C.I.	P. value
Vitamin d	0.878	0.812-0.949	<0.001	0.861	0.790-0.938	<0.001
Age	1.050	0.860-1.283	0.63	1.041	0.820-1.318	0.74
Sex	1.440	0.612-3.380	0.40	1.380	0.508-3.765	0.50
Bmi	0.930	0.802-1.081	0.35	1.001	0.844-1.190	0.99
Height	0.995	0.969-1.O20	0.73	0.970	0.929-1.016	0.21
Weight	1.001	0.976-1.028	0.91	1.041	0.995-1.088	0.08

Table-4: Logistic regression model for pain score > 6

Image-1: Wong baker faces pain rating scale

We enrolled 92 subjects with growing pains of either sex and age group of 5 to 12 years. The children with age group greater than 5 years were included as they could use pain scale easily. In our study the mean age of subjects was 7.72 years which is comparable to 7.8 years in a similar study conducted in Turkey by Aysel et.al.[20] In their studies Sobia Qamar et al[21] and Asadi Pooya et al[22] also noted a mean age of 8.05 and 7.88 years respectively. Sunil Joghee et al[23] from their study in Delhi, India reported a mean age of 9.6 years, this can be attributed to lesser number of patients (n= 45) in their study. Min Jung Park et al[24] from Korea reported a mean age of 5.2 years, but they had included children of age group 2-15 years which explains lower mean age.

In our study 61% subjects were males and 39% were females. El Metwaly at al[25] reported that girls experienced idiopathic musculoskeletal pain more frequently than boys. Sobia Qamar et al[21] reported gender distribution as 41% males and 59% females. Whereas Paladino et al[26] reported no relationship between gender and idiopathic musculoskeletal pain, Joghee et al[23] in their study found 55% were males and 45% were females which is comparable to our study. This male predominance could be due to our social setup in which males are more frequently brought to medical attention by parents then females and also due to higher outdoor activities in males. We observed no relationship of GP with age, sex, weight, height and BMI. Children with vitamin D insufficiency are at greater risk of stunted growth. In our study children had relatively lower heights, weights and

BMI but all these variables were in normal ranges. Aysel et al[20] and Sunil Joghee et al[23] also in their studies did not report any relationship of growing pains with age, sex, height and BMI. Our results are consistent with their findings.

We observed that 13% of subjects had pain in afternoon, 66% in evening and 21% during night hours. Aysel et al reported similar results in their study.The frequency of pain occurrence in our study was once a week in 4.3%, twice in a week in 13%, more than twice a week in 33.7 % and every day in 49%. Compared to findings of Aysel et al[20] the occurrence of pain in our study group was more frequent and it is possibly because of lower baseline vitamin D levels in our study group compared to their study group. We found 17.4 % subjects had pain in popliteal fossa, 18.5 % had pain in back of thigh, 46.7 % had pain in calf muscles and 16 % subjects had pain in knees and anterior thigh. Our findings were similar to the findings of Aysel et al. In their study AsadiPooya et al[22] documented pain in popliteal fossa and calf muscles in 78% subjects which is comparable to 64 % (combined calf and popliteal fossa) in our study. We noted 84 % subjects used massage for pain relief and 72 % used analgesics. The results were consistent with other studies.[20,22]

The main role of vitamin D is considered to be the regulation of calcium and phosphate metabolism.[12,13] Bone turnover markers, generally advised routinely include serum calcium, Phosphate and ALP and are considered to be reflective of the bone mineral homeostasis. Several decades ago, GP were said to be a manifestation of calcium deficiency by Abraham Jacobi. He also suggested an etiological similarity between GP and nocturnal cramps in adults due to calcium deficiency.[27] Sobia Qamar et al[21] has shown a 25% prevalence of hypocalcemia, Marwaha et al[67] had shown a decreased serum calcium levels in 21% and increased ALP in 1.6% patients. Aysel et al[20] has reported hypocalcemia in < 1 % patients. In our study we found that levels of serum calcium, serum phosphate and serum ALP were in normal range in all subjects. SakruHatun et al[28] found in their observational study about hypovitaminosis D that the serum calcium, serum phosphate and ALP were in normal range in all patients and their results are comparable to our findings.

Zargar A.H et al[29] have noted a 76% prevalence of vitamin D insufficiency in adult healthy Kashmiri population. There is no study about prevalence of vitamin D deficiency in paediatric age group of our region. In this study we found that 87% of children with GP had hypovitaminosis D. Sobia Qamar et al[21] from Pakistan have reported that 94% children with GP had vitamin D insufficiency. A similar study conducted in Korea by Min Jung Park et al[24] documented a 60% prevalence of hypovitaminosis D in children with Idiopathic musculoskeletal pain (IMSP). Our results are comparable with findings of Sobia Qamar et al.[21] The discrepancy in results compared to Min Jung park et al[24] can be attributed to the fact that they have used the term of Idiopathic musculoskeletal pain which is a wider entity encompassing both well-defined GP as well as other ill-defined limb pains. Vitamin D may not have a relationship with these ill-defined musculoskeletal pains as it has with GP.

We hypothesized that hypovitaminosis D may have a role in the pathogenesis of growing pains (GP), and that vitamin D supplementation might affect the bone and muscle status and decrease intensity of pain in children experiencing these pains. After vitamin D supplementation, we observed a significant reduction in pain intensity in children with GP, this could be attributed to a greater amount of mineralized cortical bone since it is reported in the literature that skeletal pain could be caused by an altered structure of cortical bone. Specifically in a state of vitamin D insufficiency, through PTH action, osteoblasts continue to deposit a collagen rubbery matrix on both the endosteal and periosteal surfaces of skeleton; this matrix expands under the periosteal covering and could cause an outward pressure on periosteal sensory pain fibers causing pain.[9] The baseline mean vitamin D level in our study subjects was 10.08±3.24 ng/ml with baseline mean pain score of 7.7. GraziaMorandi et al[30] reported baseline mean vitamin D level of 15.7 ng/ ml with a mean pain Score (VAS) of 7.5. Aysel et al[20] reported a mean vitamin D level of 13.4 ng/ml with a baseline mean pain score (VAS) of 6.8. In our study the mean vitamin D level was lower compared the other two studies and the severity of pain was also higher in our study group. This relationship of higher pain severity with a lower vitamin D level and vice versa in our study is comparable with these two studies.

Post vitamin D therapy, all patients (100%) had sufficient vitamin D levels. We found a vitamin D level improvement to a mean of 34.60±6.6ng/ ml (at one month). GraziaMorandi et al[30] reported a significant improvement in vitamin D level after supplementation to a mean of 34.1 ng/ ml which is comparable to our results. Aysel et al[20] noted a mean follow up vitamin D level of 44.5ng/ml. The higher mean level of vitamin D in the study of Aysel et al[20] is possibly because of higher mean baseline vitamin D level in their study group.

We believe that our study is one of the few studies to examine the effect of vitamin D treatment in children with growing pains using a pain scale (WONG BAKER FACES PAIN RATING SCALE). Wehby et al[31] used a VAS to measure health-related quality of life in children with oral clefts. Dhanani et al[32] used a VAS to determine the difference in pain associated with changes in quality of life in children with rheumatic disease. The authors concluded that the VAS can be accepted as a valid and reliable method of assessing pain in the paediatric population, especially when children are adequately educated to use it correctly. In our study the age group of 5 to 12 years was included because they could understand pain scale easily at baseline and reproduce it at follow up.

The pain score in our study dropped from of a mean of 7.7 (baseline) to 1.4 (at 3 months) and the difference was significant ($p<0.001$). Aysel[20] reported a pain score improvement from 6.8 to 2.9. GraziaMorandi et al[30] reported a pain score improvement from 7.5 to 2.2. Our results were consistent with earlier findings. In our study 31% patients had no pain at 3 months, 63% had partial improvement, no pain relief was seen in 5 % patients and 1 patient had an

increase in pain severity compared to his baseline score. Aysel et al have reported similar results. During follow up no patient developed hypercalcemia or vitamin D toxicity.

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