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Correlation between Serum Alkaline Phosphatase and Vitamin D3 Levels among 1-14 Years Old Malnourished Children: A Descriptive Observational Study

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ABSTRACT

Background and Objective: Vitamin D deficiencies are highly prevalent globally, but the correlation between serum alkaline phosphatase and vitamin D3 deficiency among Indian children is seldom investigated. To describe the correlation between vitamin D3 levels and serum alkaline phosphatase levels among children admitted to malnutrition in the pediatric wards in the tertiary care center.

Methods: This descriptive observational study was conducted among 250 malnourished children aged between 1–14-years, attending the outpatient department of a rural tertiary care center in Faridabad, Haryana. The study was conducted from February 2019 to March 2020. A detailed history was taken using a questionnaire administered to the parents/guardians of the enrolled children. Demographic data, serum alkaline phosphatase, and vitamin D3 levels were used for analysis. The collected data were transferred and analyzed in coGuide software.

Findings: The mean age of children was 6.32 ± 4.15 years (range 1-14 years). More than half (64.50%) of all malnourished children were males. Mean serum alkaline phosphatase levels were 226.95 ± 169.39 u/l (range 89 - 2341), and the mean serum vitamin D3 levels were 19.79±11.99 ng/ml (range 5.49 to 69.53 ng/ml). A weak negative correlation between serum alkaline phosphate (U/L) and serum vitamin D3 (ng/ml) (r_s: -0.105, P: 0.118) was observed.

Conclusion: There is a negative correlation between serum alkaline phosphate and serum vitamin D3. As vitamin D3 levels are low in malnourished children, active surveillance and aggressive management are the need of the hour.

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Introduction

Vitamin D, a steroid hormone also known as sun vitamin, is historically associated with regulating calcium metabolism at the bone level and has recently been strongly involved in many biological processes [1]. More than 1 billion children and adults worldwide are affected by this global health issue. Vitamin D insufficiency is often associated with neuropathy, malignancy, infertility, cardiovascular diseases, kidney diseases, glucose metabolism, and immunological dysfunctions [2]. Vitamin D, which is necessary for bone metabolism, is converted in the liver into 25-hydroxyvitamin D (25[O.H.] D) and then converted into 1, 25-dihydroxy vitamin D in the kidney to be metabolically active. So, the liver and kidney play vital roles in vitamin D activation [3].

Levels of 25- hydroxyvitamin D [25(O.H.) D] are most often used to assess the adequacy of vitamin D stores. While there is no consensus definition of vitamin D status, 25(O.H.)D level w75 nmol/L has traditionally been defined as sufficient, v50 nmol/L as deficient, and between 50-75 nmol/L as insufficient [4]. Various studies across the world, including India, have estimated the prevalence of Vitamin D deficiency in healthy children to be in the range of 10–90%, owing to inadequate sunlight exposure because of an indoor lifestyle, use of sunscreens, high levels of skin pigmentation, and insufficient dietary sources of vitamin D [5].

Malnourishment is likely to be associated with vitamin D intake deficiency. Though there is sufficient ultraviolet (UV) exposure, there seem to be low serum vitamin D concentration levels in some individuals due to variations in levels of skin pigmentation. Worldwide, more than half of deaths in children are due to malnourishment, the most critical risk factor for illness and death globally [6]. Total alkaline phosphatase (ALP) and bone alkaline phosphatase (BALP), measured either as protein concentration or as enzyme activity, are widely used as bone formation markers, particularly in patients with primary and secondary bone diseases and calcium-phosphorus homeostasis disturbances [7]. Compared to average age- and sex-matched populations, total ALP levels are significantly higher in individuals with vitamin D deficiency, rickets, osteomalacia, hyperparathyroidism, and Paget's disease. BALP levels are elevated, especially during rapid physiological bone growth in children and adolescents, and acromegaly is associated with growth hormone excess. Hypervitaminosis D, hypophosphatasia, malnutrition, magnesium deficiency, and hypothyroidism are associated with decreased bone formation and, consequently, ALP and BALP activity [8]. Vitamin D, necessary for normal calcium-phosphorus homeostasis and skeleton mineralization, also influences bone turnover during growth [9].

A previous cross-sectional study by Nabeta HW et al.[10] In Uganda, among 158 6- to 24-month-old children, there was no statistically significant difference in vitamin D values between the malnourished and non-malnourished children, and suggested that clinicians should actively screen for children for serum vitamin D levels regardless of nutritional status. Yeşiltepe-Mutlu G et al.[11], in his population-based study in Turkey, showed a significant correlation of serum 25-OHD concentrations with ALP only in the adult population (>18 years). The mean ALP levels were similar across the different vitamin D status groups.

Vitamin deficiencies are common in children with malnutrition, and, as a result, they may suffer from various nutrient-specific deficiency disorders. Vitamins are required for the functioning of several enzymes like serum alkaline phosphatase and their deficiency could alter the functioning of the enzyme. In developing countries like India, there is insufficient data regarding the correlation between vitamin D deficiency and serum alkaline phosphatase levels among children admitted with malnutrition and their correlation with laboratory parameters. Hence, the present study was undertaken to describe the correlation of vitamin D levels and serum alkaline phosphatase levels among children admitted with malnutrition to the pediatric wards of the tertiary care teaching center. The aim of this study was to describe the correlation between vitamin D levels and serum alkaline phosphatase levels among children admitted with malnutrition to the pediatric wards of the tertiary care teaching center.

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Methods

Study design and participant

This descriptive observational study was done on children visiting the department of pediatrics at a tertiary care teaching center in Faridabad, Haryana from February 2019 to March 2020. Inclusion criteria were children aged 1 to 14 years with evidence of malnourishment for a period longer than three months. Children with consumption of fish oil, vitamin D, mineral supplements, fortified formula milk, and obese children whose parents/guardians did not give informed consent were excluded from the study. For the feasibility of the study, convenience sampling was applied.

Data collection:

A questionnaire consisting of a detailed history regarding socio-demographic data was given to the parents/guardians of the enrolled children. Using standard techniques, the physical examination was then performed on every child to record weight, height, length, left mid-upper-arm circumference, chest circumference, and head circumference.

Evaluation of malnutrition

Based on anthropometric findings, children with malnutrition were categorized depending on the measurements of weight-for-height and weight-for-length. Based on the World Health Organization (WHO) reference Z score, malnourished children were either classified as severe acute malnutrition (SAM) or moderate acute malnutrition (MAM) [12]. MAM -<2 and up to −3 SD, SAM -<3 SD. The non-malnourished children were usually defined by the Z score, above −1 S.D.

The term malnutrition addresses 3 conditions:

- **Undernutrition** – This group includes wasting (low weight-for-height), stunting (low height-for-age) and underweight (low weight-for-age);
- **Micronutrient-related malnutrition** – This group includes micronutrient deficiencies (a lack of important vitamins and minerals) or micronutrient excess; and
- This group includes overweight, obesity, and diet-related non-communicable diseases (such as heart disease, stroke, diabetes, and some cancers.

Lab investigations

Alkaline phosphatase was evaluated and expressed in U/l. Enzyme-linked immunoassays were used to determine serum vitamin D levels 25(O.H.). Children with vitamin D levels of <12 ng/ml were categorized as vitamin D deficient, while those who had (12-20 ng/ml) as insufficient and sufficient levels were designated as > 20 ng/ml [13, 14]. An alkaline phosphatase level >350 U/l was considered to be abnormally high.

Statistical analysis

Quantitative variables were represented as mean and standard deviation (S.D.). The association between quantitative explanatory and outcome variables was assessed by calculating the Spearman rank correlation coefficient (rs) and represented a scatter diagram. In all tests, a P-value was considered significant if <0.05 and analyzed using R studio and coGuide software.

Results

All 231 subjects were included in the final analysis. The mean age was 6.32 ± 4.15 years (range 1-14 years). Most of the study participants were male, 149(64.50%) and 82(35.50%) participants were females.

Mean serum alkaline phosphatase levels were 226.95 ± 169.39 u/l (range 89 - 2341) and the mean serum vitamin D3 levels were 19.79 ± 11.99 ng/ml (range 5.49 to 69.53 ng/ml). The mean serum Ca2+ was 8.25±0.26 mg/dL (ranged from 7.1 to 8.9) and the mean serum mag2+ was 1.93±0.15 mg.dL (ranged from 1.7 to 2.8). (Table 1).

There was a weak negative correlation between serum alkaline phosphate (U/L) and serum vitamin D3(ng/ml) (r_s: -0.105, P =0.118). (Figure 1).

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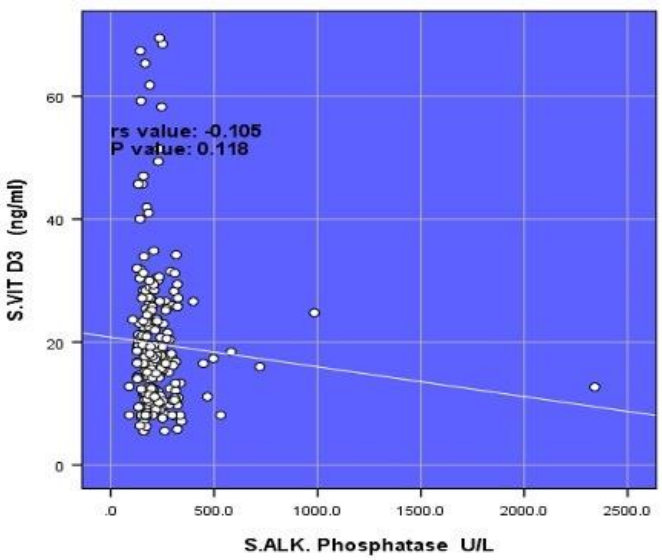
Table 1. Summary of baseline parameter (N=231)

Parameter		Summary
Age (in years)		6.32 ± 4.15(ranged from 1 to 14)
Gender	Male	149(64.50%)
	Female	82(35.50%)
Lab parameter	S. Alk. Phosphatase (U/L) (N=229)	226.95 ± 169.39(ranged from 89 to 2341)
	Serum vitamin D3 (ng/ml) (N=226)	19.79 ± 11.99 (ranged from 5.49 to 69.53)
	S. Ca2+ (N=231)	8.25 ± 0.26 (ranged from 7.1 to 8.9)
	S. Mag2+ (Mg/Dl) (N=230)	1.93 ± 0.15 (ranged from 1.7 to 2.8)



Figurer1. Correlation between serum alkaline phosphate (U/L) and serum vitamin D3 (ng/ml)

Discussion

The present study reported a correlation between serum alkaline phosphatase and vitamin D 3 levels in 1-14-year-old malnourished children attending rural tertiary care centers in Faridabad, Haryana. The mean age for both sexes was 6.32 ± 4.15 years (range 1-14 years). More than half, 149 (64.50%) of all malnourished children were males. There was a weak negative correlation between serum alkaline phosphate (U/L) and serum vitamin D3 (ng/ml) (r_s value: -0.105, P-value: 0.118).

The present study's mean age was 6.32 ± 4.15 years (range 1-14 years). More than half (64.50%) of all malnourished children were males. The finding was similar to a study by Kumar D et al. [15] in India, where out of 384 patients, the mean age was 5.7± 3.7 years, of whom 208 were boys. In the present study, the mean serum vitamin D3 levels were 19.79 ± 11.99 ng/ml (5.49 to 69.53 ng/ml). This was almost similar to the findings of a study by Ananda Kesavan TM et al. [16] from Kerala, India, where the mean (range) Vitamin D level was 18.1 (3.7- 68.0) ng/ml. In the current study, the mean serum alkaline phosphatase levels were 226.95±169.39 u/l (range 89-2341). The levels were more significant when compared to a descriptive cross-sectional study in Tanzania by Walli NZ et al. [17], where the mean (6SD) alkaline phosphatase levels were 176.6 U/l±133.1. Previous studies have found that biochemistry has little diagnostic value in malnourished children, as malnutrition could alter their biochemical changes [18]. The mean serum calcium level in the present study is similar to the study of Ananda K et al. (9.0 mg/dL) [16].

In the present study, there was a weak negative correlation between serum alkaline phosphate (U/L) and serum vitamin D3 (ng/ml) levels (r_s value: -0.105, P-value: 0.118). This can be due to changes in ALP concentrations during infancy and childhood. Yeşiltepe-Mutlu G et al. [11], in their nationwide study in Turkey, reported a similar finding, where vitamin D levels showed an inverse

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correlation with ALP levels in the pediatric age group. Another study in India by Sarma D et al. [19] showed a significant negative correlation of vitamin D levels with BMI, and alkaline phosphatase, similar to the present study.

In the present study, malnourished children had altered vitamin D levels and serum alkaline phosphatase levels. A study by Jones KDJ et al. [20] in Kenya found that 71% of children had serum 25-hydroxyvitamin D levels below 30 nmol/L. These results suggest that rickets in young children in urban Kenya are usually driven by vitamin D deficiency and vitamin D supplementation is likely required for a full recovery. These findings contrast a study in Vietnam by Chuc D Van et al. [21], where malnutrition was not statistically different with sex and age group. This difference in findings and other studies was because the present research subjects lived in areas with different socioeconomic conditions and were vulnerable to various risk factors. Witkowska-Sędek E et al. [22] found that vitamin D deficiency is widespread. Its supplementation is necessary for all children and adolescents to enhance the effects of growth hormone (rhGH) therapy. The supplementation also contributes to a significant increase in bone formation that decreases bone disorders.

The present study provided relevant insight into, the correlation of serum ALP and vitamin D3 among 1–14-year-old malnourished children. In India, malnutrition is still a significant public health problem. This condition can be controlled by reducing the percentage of low-birth-weight babies, increasing female literacy, and expanding and promoting health-seeking behavior in the community. Mothers need to be educated regarding the benefits of exclusive breastfeeding of the child for the first six months of life, the importance of initiation of complementary feeding after 6 months of age, and the complementary feeds need to be hygienically prepared [23].

Conclusion

The low vitamin D3 in malnourished children underlines the need for active surveillance and aggressive management. There was a negative correlation between serum alkaline phosphate and serum D3 levels. The children's nutritional status should be explained to their parents and local health service leaders to intervene to address malnutrition at the earliest. In improving overall nutritional status and particularly addressing vitamin D deficiency and malnourishment, some community-based interventions should be implemented at primary, secondary, and tertiary care levels of prevention.

Limitations

The study had a few limitations. The data reported was from a single rural tertiary care center, which may be inappropriate to generalize the findings. The other limitations were the lack of data regarding the time of day the samples were taken, clinical status, lifestyle, breastfed, and weaning time. A detailed nutritional analysis was not performed. The low rate of concurrent ALP measurement caused difficulties in interpreting the severity of vitamin D deficiency and its correlation. The results of the present study call for more future multicentric studies targeting research into the impact of malnourishment among children and also to generate better data regarding the correlation of serum alkaline phosphates and vitamin D levels.

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Ethical approval

The institutional review board of the concerned center approved the study. Parents/guardians of children had given written informed consent. Confidentiality was maintained throughout the study.

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Conflict of interest

The authors declare that there is no conflict of interest.

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