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# Biochemical and Radiological Markers Of Vitamin D Deficiency In Children With Severe Acute Malnutrition And Its Correlation With Serum Vitamin D Levels

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**Abstract**

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## Introduction

There is high prevalence of Vitamin D deficiency in children with severe acute malnutrition (SAM) which range from 34 % to 65 % according to previous studies [1,2,3]. Vitamin D causes increased absorption of calcium (Ca) and phosphorus from intestine and kidney and Parathyroid hormone (PTH) causes loss of phosphorus and increased absorption of calcium from kidney. Initially calcium levels are maintained in vitamin D deficiency due to secondary increase in PTH. Increased PTH causes normalization of calcium, loss of phosphorus and increased bone resorption leading to soft bone. In prolonged vitamin D deficiency (VDD) states, the parathyroid becomes refractory, leading to both hypocalcemia and hypophosphatemia [4].

Along with controlling the calcium and phosphorus homeostasis, vitamin D also maintains neuromuscular and cellular function like immune regulation and insulin production. Immunomodulatory function of vitamin D may lead to increase in various complications in children with SAM. Prolonged deficiency may also affect the linear growth [5]. Supplementation of 400 IU vitamin D is now recommended in less than 1 year old SAM Children but not in those whose age is beyond 1 year. Estimating vitamin D levels in all SAM children would be expensive in resource limited setting. Biochemical markers of VDD can be used as a cheaper screening tool to identify this condition. So, we aim to look for correlation between biochemical markers of VDD and its levels in children with SAM.

## Methods

All children with SAM aged 1 to 60 months admitted in Nutritional rehabilitation center (NRC) of tertiary care center in Eastern UP from August 21 to June 22 were enrolled in this study. SAM was defined as Weight for height (W/H) below -3 standard deviation (SD) of median WHO (World Health Organisation) growth reference and/or Mid upper arm circumference (MUAC) below 11.5 cm and /or Presence of bipedal edema. WHO criteria for identifying SAM in infants <6 months of age- Any infant more than 49 cm in length who has: W/H < -3 SD of median WHO child growth standards and /or Visible severe wasting and/or Edema of both feet. Children with major congenital malformations, chronic systemic diseases such as chronic kidney disease, chronic liver disease, Global developmental Delay, unstable parameters on admission, hypothyroidism and whose height for age is more affected than weight for age were excluded.

*Data collection*: After taking a detailed informed consent, clinical and the demographic information were recorded on a pre-structured proforma, together

with the detail history, physical and detailed systemic examination. Weight of the child was measured by electronic weighing scale. Infant or the child was made naked or minimally clothed. Length was taken up to 2yrs of age. It was measured by infantometer. Infant was made to lie straight with his shoulder and buttocks flat against the measuring surface. Body was aligned in a straight line with eyes looking upwards. A second person was asked to hold the head of the child to touch the head piece, preferably mother. The examiner extended both legs by one hand on knee, and bringing the foot piece firmly against the heels. Length was measured to the nearest 0.1cm. Height was measured by stadiometer in children above 2yrs of age. Child was made to wear only minimum clothing without shoes and socks and made to stand with feet parallel on an even platform. Child's head was adjusted to be at the Frankfort plane. Head, shoulder blade, buttocks and heels were made to touch the measuring surface. The head piece was lowered to touch the top of the head. Measuring accuracy was 0.1cm. Mid Upper arm Circumference (MUAC) was measured at left upper arm midway between acromion and olecranon process. Clinical signs of rickets such as Wrist widening, Rachitic rosary, bowed legs, double malleoli or Harrison's groove, pot belly were noted. Socioeconomic status of study subjects was assessed according to Modified Kuppuswamy scale of social classification. Nutrition and dietary assessment were done according to Infant and Young child feeding practices (IYCF) [6].

*Laboratory Investigation*: 25-Hydroxyvitamin D (25OH D) levels were estimated by using Electrochemiluminescence immunoassay (ECLIA). Levels <20 ng/ml and between 21-29 ng/ml were defined as Vitamin D deficiency and insufficiency, respectively [7]. Ionic Calcium estimation was done by Spectrophotometry-OCC method. Ionized fractions of less than 1.1mmol/L were taken as hypocalcemia. Serum phosphate levels were measured by Spectrophotometry-Phosphomolybdate reduction method and levels less than 4.5mg/dL was defined as hypophosphatemia. Normal ALP were taken as 90-180 U/L and 139-260 U/L in children between 1 month-3 years and in children between 3 to 5 yrs. respectively. X-ray of left wrist AP view was done to look for signs of Rickets such splaying, fraying, or cupping.

*Statistical analysis*: Data was statistically described in terms of mean± standard deviation, median and range, or frequencies and percentages when appropriate. Comparison between discrete variables was done using chi-square and Fisher's exact tests for categorical data. p values less than 0.05 was considered statistically significant. Correlation between vitamin D and Hypocalcemia in severe acute malnutrition patients were estimated by Spearman's rho correlation coefficient.

## Results

A total of 70 children enrolled in study whose mean age was 21.29+12.83 months with male to female patients was 1.5:1. Most of the children (81.4%) belonged to lower middle socio-economic class in our study. There were 28 (40%) SAM children who were edematous and oedema was significantly related to VDD in our study (p value=0.027). Among 17 (24.3%), severe anemia was noted, but it was not significantly related to VDD (p value=0.157). Among VDD deficient group, Early initiation of breast feeding was not done in 75% patients (p value=0.585). VDD was significantly more common in non-breastfeeding infants (p value=0.006). Timely initiation of complementary feeding was not significantly associated with VDD (p value=0.42).Eighteen out of seventy children had one or more signs of rickets on X-ray, which was statistically significant (p value=0.002). Among vitamin D deficient children, only six children had cupping, three had fraying, 6 had splaying. The baseline characteristics are given in Table 1.

Mean vitamin D levels were 22.93+12.24ng/ml. Vitamin D deficiency, insufficiency and sufficiency was found in 40 (57.1%), 12 (17.1%), 18 (25.7%) children respectively. Serum calcium and phosphorus levels are given in Table 2.

In majority of SAM patients, Anemia (22,31.4%) and respiratory infections (22,31.4%) were common complications. Among vitamin D deficient patients, around 43% were anemic, 20% had diarrhea or dysentery, 30% had respiratory infections (p value=0.158).

Sixty- three (90%), 2 (2.9%), 2 (2.9%), 1 (1.4%) and 2 (2.9%) children got cured, failed, died, transferred, and left treatment (defaulter) respectively. Mortality was observed among 3% children. Among vitamin D



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deficient children, 85% got cured and death occurred in children with VDD. Both, non-responder, and defaulter children were VD deficient. There was no significant association of VDD with respect to poor outcome (p value=0.773).

Sixty-eight (97.1%) SAM children had weight for height (W/H) less than -3SD (severe wasting), 62 (88.6%) had weight for age (W/A) less than -3SD and 29 (41.4%) had height for age (H/A) less than -3SD (severely stunted). There was no significant association of severe stunting with VDD (p value=0.340).

**Discussion:**

Prevalence of VDD in our study was 57.1%. Several previous studies also showed that VDD in SAM children range from 30-70% [1,2,3]. We did not find any significant relation of birth weight, gestational age, and mode of delivery with vitamin D levels. But study done by Burris HH et al., (2014) showed that preterm babies are at increased risk of vitamin D deficiency [8]. The difference could be because most children were of higher age group in our study. We did not find any significant relation of maternal age, parity, and maternal education with vitamin D levels in children. Study done by khalessi N et al., (2015) in Tehran-Iran showed that there was significant relation between high maternal age and vitamin D deficiency. The difference could be because in India there is custom of early marriage and we had most of the mothers who were young. They also found no relation of parity and maternal education with vitamin D levels, like our study [9]. We did not find any significant relation of number of ANC visits, IFA supplementation and calcium supplementation with levels of vitamin D in SAM children. Study done by Pehlivan I et al., (2003), showed that there was no significant relation with maternal and infant vitamin D levels, like our study [10]. A metanalysis done by karras SN et al., (2016) showed that there is significant impact of maternal vitamin D on birth weight and bone mass of offspring [11]. There was no significant relation of most of IYCF indicators with vitamin D levels except for EBF (p value=0.006). Study by PS P et al., (2017) showed that nonexclusive breastfeed may lead to suboptimal vitamin D levels and increased risk of pneumonia. This emphasizes the role of exclusive breastfeeding in these children [12]. Vitamin D has immunomodulatory function and those children who are already vitamin D deficient may develop more severe disease thus landing into edematous SAM. This could be the reason that we had significant relation between VDD and edema. Study done by Kumar D et al., (2020) also showed that hypocalcemia (which is a close biochemical marker of VDD) was 1.6 times more common in children with edematous SAM [13]. A multicentric study done by Khadilkar A et al., (2017) found that VDD was more common in low socioeconomic status [14]. But we did not find any relation between SES and VDD as we only enrolled children with SAM in whom most belonged to lower middle and lower upper lower. We found a positive correlation between hemoglobin levels and vitamin D levels in our patients indicating multiple micronutrient deficiency in these children. A meta-analysis done by Arabi SM et al (2020) also showed that there is a high risk of developing anemia in a person with VDD[15]. Faulty feeding and infections in SAM children could be the reasons for coexistence of two conditions.

Hypocalcemia and hypophosphatemia are important biochemical findings in children with VDD. Hypocalcemia is a finding of prolonged VDD, initially body tries to maintain calcium response by secondary increase in PTH hormone. The prevalence of hypocalcemia in our study was 51.4% (N=36) and out of them 86% (N=31) children had VDD. We found a significant correlation between hypocalcemia and hypophosphatemia with VDD. Hypocalcemic children who were not VDD could be because of dietary calcium deficiency. This may also lead to rickets and effects bone health. The prevalence of hypocalcemia in several previous studies ranged from 26-71% [2, 13,16]. Smilie C et al., (2020) in their study also showed that hypocalcemia was present in 26% children with SAM and 76.9% of these children also had VDD [2]. There are various sources of ALP in body like bone, liver, kidney, placenta etc. Ninety percent of vitamin D deficient and hundred percent of VD insufficient children had raised ALP levels, but ALP was not significantly related to VDD. Nahida ZW et al., (2017) also showed poor correlation between ALP levels and VD levels [17]

X ray findings of rickets were observed in only 22.8% (N=16) SAM children. Xray features of rickets were significantly related to VDD. Only 17 (42 %) of the VDD children had X ray features of rickets. and clinical features of rickets were found only in 7 (17 %) of the VDD children. This explains that we cannot rely



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only on Xray and clinical features of rickets for diagnosing rickets in children with SAM. Several previous studies in SAM children showed that prevalence of radiologically confirmed rickets ranged from 13% to 40% [17, 18,19]. Study done by Jones KD et al., (2018) showed significant relation of VDD and Xray findings of rickets like our study [20]. Less prevalence of radiological features of rickets in children with SAM as compared to general population (60-90%) was because, rickets is a disease of growing bones and SAM is a condition in which growth is hampered. So, even after VDD only 42% children had X-ray features.

About 92% of SAM children were moderate to severely stunted and 88% of SAM children were severely underweight as well. This indicated their chronic malnutrition status. We did not find any significant relation of vitamin D levels with stunting (p value=0.340). Rana M et al. (2017) showed that underweight children are more prone to have VDD and VDD children have more stunting against our study. This may be due to absence of control group in our study**.** Metanalysis by Song C et al., (2021) also did not find any association of vitamin D levels with stunting and underweight [21].

We did not find any association of outcome of children of SAM with VDD although we did look for duration of stay in these children.Banna SE et al., (2020) in his study showed that severe malnutrition and vitamin D deficiency at PICU admission was prevalent in critically ill children and was associated with adverse clinical outcomes such as intubation and prolonged PICU stay [22]. Cariolou M et al., (2019) in his study showed that VDD in acute and critically ill children is high and is associated with increased mortality. the difference in our study was due absence of control group look for outcome [23].

**Conclusion**: VDD is common in children with SAM. Hypocalcemia and Hypophosphatemia are cheaper and good screening tool for diagnosing it, as clinical and radiological markers may not be significantly evident in these children.

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**Table 1: Base line characteristics of patients**

| Base line characteristics | Value |
|---|---|
| Residence of patients | 35 (50%) from Prayagraj |
| Low birth weight | 37 (52%) |
| Preterm delivered babies | 11 (16%) |
| Incomplete immunization | 32 (46%) |
| Mean maternal age | 26.47 ±2.98 years |
| Literacy rate in mothers | 48 (70%) |
| At least 3 Antenatal visits in mother | 21 (30%) |
| Calcium supplementation taken during pregnancy | 54 (77%) |
| Early initiation of breastfeeding | 18 (25%) |
| Exclusive breastfeeding rate | 23 (33%) |



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| | |
|---|---|
| Timely initiation of complementary feeds | 19 (27%) |
| Minimum meal frequency | 11 (16%) |
| Minimum dietary diversity | 9 (13%) |
| Clinical features of rickets | 11(15%) |
| Motor delay in children | 14 (20%) |
| Anemia | 17 (24.3%) |
| Edema | 28 (40%) |
| Radiological Features of Rickets | 18 (25.7%) |

**Table 2: Calcium and phosphate levels in patients**

| | | **VITAMIN D LEVELS** | | | | | | | | **p-value** |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **<20- Deficiency** | | **21-29- Insufficiency** | | **30-150 Sufficiency** | | **Total** | | |
| | | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | |
| HYPOCALCEMIA | <=1.1- Present | 31 | 77.5% | 4 | 33.3% | 1 | 5.6% | 36 | 51.4% | **<0.001** |
| | >1.1- Absent | 9 | 22.5% | 8 | 66.7% | 17 | 94.4% | 34 | 48.6% | |
| HYPOPHOSPHATAEMIA (<4.5mg/dL) | <4.5 mg/dL: Present | 32 | 80.0% | 5 | 41.7% | 1 | 5.6% | 38 | 54.3% | **<0.001** |
| | >4.5 mg/dL: Absent | 8 | 20.0% | 7 | 58.3% | 17 | 94.4% | 32 | 45.7% | |

**Table 3: Correlation of Vitamin D deficiency with biochemical parameters**

| **Parameters** | **Spearman's rho correlation coefficient** | **p-value** |
|---|---|---|
| Hemoglobin (g/dL) | .344 | **0.004** |
| TLC (cells/mm3) | -0.014 | 0.906 |
| S. Sodium (mmol/L) | 0.037 | 0.762 |
| S. Potassium (mmol/L) | 0.212 | 0.079 |
| S. Calcium (ionic, mg/dL) | .596 | **<0.001** |
| S. Phosphate | .673 | **<0.001** |
| S. ALP (IU/L) | -0.024 | 0.843 |
| S. Albumin (mg/dL) | 0.194 | 0.107 |
| S. proteins (mg/dL) | 0.163 | 0.178 |



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**Table 4: Anthropometric indices of patients**

| | | VITAMIN D LEVELS | | | | | | | | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | <20- Deficiency | | 21-29- Insufficiency | | 30-150 Sufficiency | | Total (70) | | |
| | | N | % | N | % | N | % | N | % | |
| Weight for age | -2SD to -3SD | 6 | 15.0% | 1 | 8.3% | 1 | 5.6% | 8 | 11.4% | 0.540 |
| | <-3SD | 34 | 85.0% | 11 | 91.7% | 17 | 94.4% | 62 | 88.6% | |
| Height for age | Median to -1SD | 0 | .0% | 0 | .0% | 1 | 5.6% | 1 | 1.4% | 0.340 |
| | -1SD to -2SD | 4 | 10.0% | 0 | .0% | 0 | .0% | 4 | 5.7% | |
| | -2SD to -3SD | 19 | 47.5% | 8 | 66.7% | 9 | 50.0% | 36 | 51.4% | |
| | <-3SD | 17 | 42.5% | 4 | 33.3% | 8 | 44.4% | 29 | 41.4% | |
| Weight for height | -2SD to -3SD | 1 | 2.5% | 0 | .0% | 1 | 5.6% | 2 | 2.9% | 0.656 |
| | <-3SD | 39 | 97.5% | 12 | 100.0% | 17 | 94.4% | 68 | 97.1% | |

**Figure 1: Correlation between serum calcium and vitamin D levels**

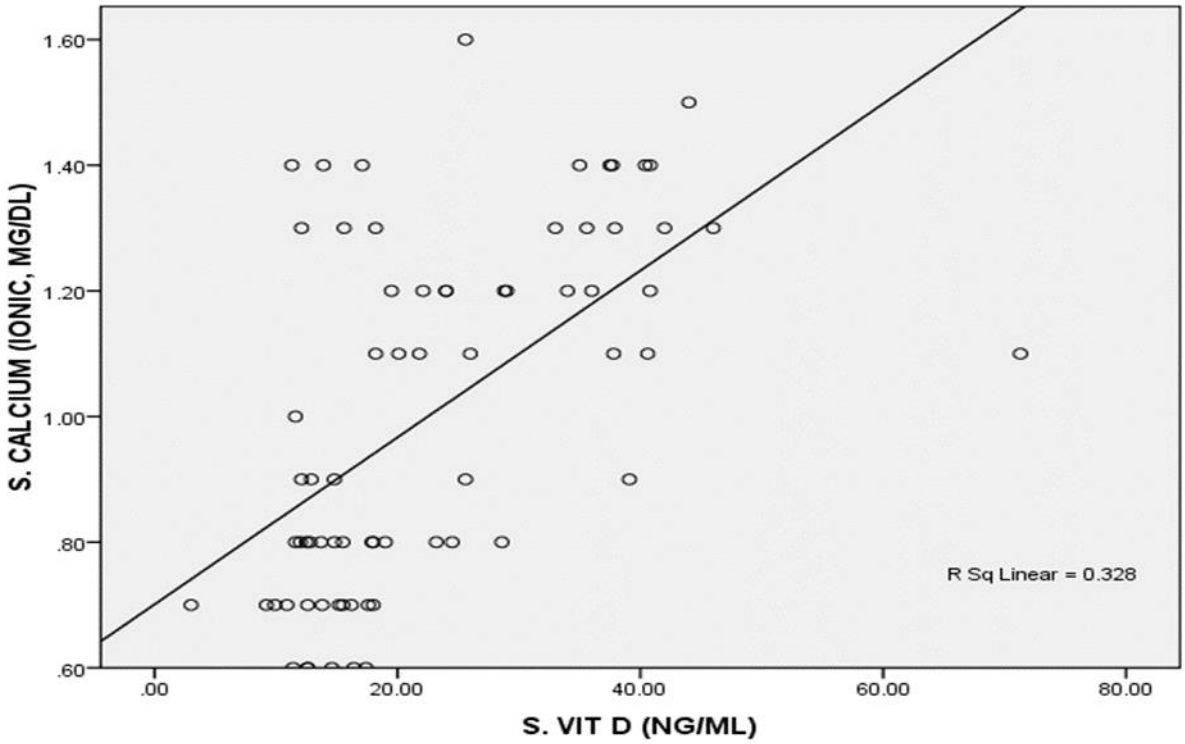


**Figure 2: Correlation between serum Phosphorus and vitamin D levels**



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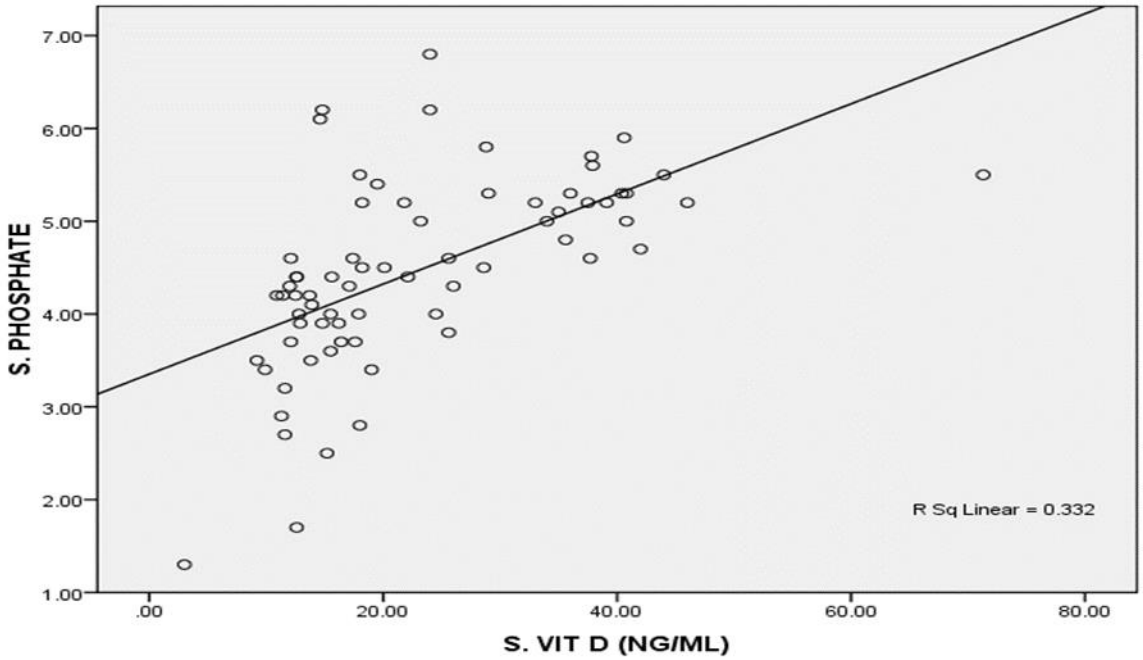




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