Original Research Article

Causes and management of nutritional rickets among paediatric age group in Rajasthan: a randomised control trial

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ABSTRACT

Background: Rickets disease frequently caused by insufficient of vitamin D. Nevertheless, subsequent researchers have attributed it to a calcium insufficiency throughout the eating plan. There is very little data on the relative efficacy of calcium, vitamin D, or both in the treatment of rickets. The goal of this study was to see if calcium, vitamin D, or a combination of the two may help young infants with nutritional rickets.

Methods: 100 patients of nutritional rickets aged 6 months to 5 years were randomly assigned to receive vitamin D (6,00,000 IU single intramuscular injection), calcium (75 mg/kg/day elemental calcium orally) or a combination. All of the participants' demographics, nutritional status, dietary calcium, and phytate consumption were evaluated.

Results: More than 80 percent of the patients in the study had 25OHD levels below 20 ng/ml. Rickets was discovered as an afterthought throughout the remaining 60. Lower respiratory illness (40), upper respiratory tract illness (10) and acute gastroenteritis have been the presenting conditions.

Conclusions: Children experiencing rickets exhibited low vitamin D levels in their blood as well as a low calcium intake from their nutrition. When compared to either vitamin D or calcium alone, the combination showed the best therapeutic effect.

Keywords: Vitamin D, Calcium, Nutritional rickets, Genu varum, Genu valgus, Sun light

INTRODUCTION

Nearly half of the world's population is vitamin D deficient. Vitamin D deficiency affects an estimated one billion people worldwide, of all ethnicities and ages (VDD).[1-3] This pandemic of hypovitaminosis D is mostly caused by lifestyle and environmental variables that limit sunlight exposure, which is required for UVB-induced vitamin D synthesis in the skin. Because black people's melanin absorbs more UVB than white people's, they require more sun exposure to produce the same amount of vitamin D.[4] Rickets, a common nutritional disorder, is often blamed on a low vitamin D level. Recent evidence from various tropical nations, however, reveals that

calcium deficiency may play a significant role in rickets development.[5-10] In Nigerian children with rickets, calcium supplementation was just as effective as a combination of vitamin D and calcium in encouraging recovery. According to research done among adults and children calcium consumption in India is well below the recommended amount.[11,12] In India, the cuisine is largely vegetarian, centred on grains and lentils, and milk and milk products are typically lacking the high number of phytates in vegetarian cuisine further compromises the diet's low calcium supply.[13] Furthermore, research from various countries throughout the world, including India, has revealed widespread vitamin D insufficiency.[14-17] Seth et al discovered serum 25-hydroxycholecalciferol D (25-

OHD) levels of 10 ng/ml in 47.8% of apparently healthy nursing mothers and 43.2 percent of their newborn babies in a recent study.[18] The relative roles of each in the genesis of rickets and the best therapeutic strategy for its treatment are unknown. We wanted to see if calcium, vitamin D or a combination of the two might help Indian youngsters recover from nutritional rickets.

METHODS

Prospective cross sectional research study carried out in the outpatient clinic in orthopaedics and paediatrics at government medical college Kota, who reported clinical and radiological evidence of nutritional rickets from December 2017 to March 2019, included 130 patients Every child's parent or guardian received informed consent before participating. The methodology was ethical clearance was obtained from ethics board

Sample Size

$$SS = Z^{2*}P^* (1 - P)/C^2$$

Where Z=Z value (e.g., 1.96 for 95°/4 confidence level), P=percentage picking a choice, expressed as decimal (0.5 used for sample size needed), C=confidence interval, expressed as decimal (e.g., 0.04= ±4). Correction for finite population is done by following formula where Pop= population.

$$new\ SS = ss/ss - 1$$

$$new\ SS = 1 + ss - 1/Pop$$

Inclusion and exclusion criteria

Inclusion criterion for current study was children between the ages 6 months to 5 years. Exclusion criteria for current study were participants with non-nutritional aetiologies (kidney or liver disease, malabsorption syndromes, anti-epileptic drug usage, chronic illness as well as hypocalcemic seizures or a history of using calcium or vitamin D supplements in the past 6 months and previous History of Trauma, to exclude out non-nutritional rickets, appropriate diagnostic tests were done when indicated.

Treatment allocation and randomization

Block randomization was used to assign the individuals to one of the following three treatment arms: Group A; 600 000 IU of vitamin D were administered intramuscularly. Group B: one intramuscular injection of 600 000 IU vitamin D and 75 mg/kg calcium, for 12 weeks, take three split dosages each day, Group C: three doses of 75 mg/kg of elemental calcium daily in split dosages for 12 weeks. Total 15 of the 130 children examined had used calcium/vitamin D supplements in the previous 6 months, 7 had a chronic medical/surgical condition, 5 were under the age of eligibility, and 3 denied permission. As a result, the study comprised a total of 100 patients.

Table 1: Demographic data (N=130).

Variables	Group A, (vitamin D alone) n=35	Group B (vitamin D+ calcium) n=30	Group C (calcium alone) n=35	Total N=100	
Lost follow-up	5	2	3	10	
Final follow-up	30	28	32	90	
Excluded cases from study	Taken supplements N=15	Chronic diseases N=7	Outside range of age N=5	Refused for consent N=3	Total N=30

Data and sample collection the recruited respondents were examined on demographic parameters such as age, gender, and monthly family income. A comprehensive nutritional evaluation was carried out, which included a history of breast-feeding and supplemented feeding. Researchers employed a 24-hour dietary recall and a meal frequency questionnaire to estimate dairy consumption of calcium, phosphates, and phytates. The current symptoms' kind, onset, and duration were also studied. The world health organization's 2006 growth reference criteria were used to calculate the Z-scores for weight and height for age.

Vitamin D metabolism

Healthy bones and teeth require vitamin D. It helps in enterocyte formation as well as calcium and phosphate uptake in the colon. Mineralization of the skeletons is aided by this. Vitamin D stimulates osteoclast activity in hypocalcemia and hypophosphatemia, bringing calcium and phosphorus levels in the body back into balance.

Hypocalcemia and hypophosphatemia are caused by vitamin D insufficiency or resistance hypocalcaemia causes the production of parathyroid hormone (PTH), which partially corrects hypocalcaemia while increasing urinary phosphate excretion, resulting in hypophosphatemia and osteomalacia. 25(OH)D is also vital for maintaining extra skeletal health. Vitamin D inadequacy has been associated with multiple sclerosis, type 1 diabetes, rheumatoid arthritis, inflammatory bowel disease, psychological illnesses, as well as carcinoma such as breast, prostate, and colorectal cancer. Hypertension, hyperglycemia, metabolic disorders, and respiratory illness have all been related to low vitamin D concentration in the blood in teenagers. Vitamin D deficiency in vulnerable groups It's challenging to provide enough vitamin D through fruits and vegetables with natural food alone.

Vitamin D deficiency may be prevented by eating vitamin D-fortified foods and getting some sun. Certain individuals may require vitamin D supplements to fulfil their basic necessities.
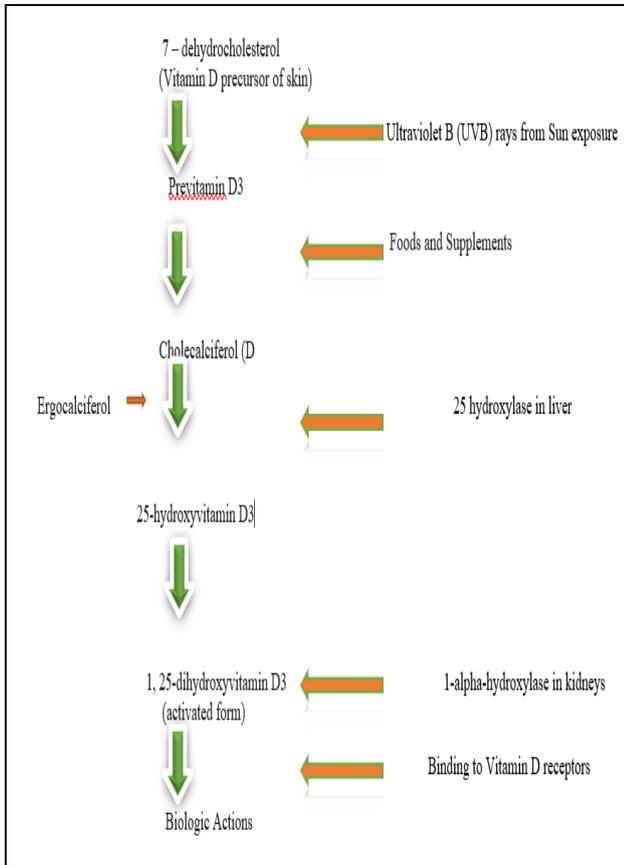

Figure 1: Vitamin D metabolism.

Causes of vitamin D deficiency

Reduced cutaneous synthesis people who do not get enough sun may develop vitamin D insufficiency. Sun exposure vitamin D is obtained by exposing a Caucasian newborn to sunshine for 30 minutes per week while just wearing a diaper or for 2 hours per week when fully dressed and without a cap. Asians require three times the amount of solar exposure, whereas Africans require six times the amount.[19,20] A sunscreen with an SPF of 8 can reduce vitamin D3 synthesis capacity by 95%, while one with an SPF of 15 can reduce it by 98 percent. Cold climates due to limited sun exposure towards the end of the winter, vitamin D insufficiency is also frequent.[21] Dark-skinned immigrants from warm regions to cold climes have been found to have vitamin D insufficiency. Asian Indian immigration to the United States Even with adequate sunlight, the United States may be deficient in vitamin D sufficient sun exposure.[22] Significant burns even with sun exposure, vitamin D production in the skin is lower in people who have had substantial burn injuries.[23] Elderly people with age, cutaneous vitamin D production and storage decrease. In older people, vitamin D levels are frequently low.

Calcium absorption is limited in older people with achlorhydria. In addition, older people may be limited to their homes.[24]

Nutritional deficiency even with ample sun exposure, vitamin D insufficiency can develop.[25] It can happen to persons who eat vitamin D deficient diets or who have intestinal vitamin D malabsorption. There are just a few foods that naturally contain vitamin D, and because the majority of them are animal or fish-based, they may not be suitable for vegetarian societies. Vitamin D is currently added to only a few foods. Fortification of milk and other foods with vitamin D should be explored. Maternal vitamin D deficiency vitamin D is transmitted from of the mother to the foetus through the use of the placenta, therefore lower vitamin D levels in the infant are related to lower vitamin D reserves with in mother.[26,27]

Low vitamin D levels during gestation have been attributed to embryonic growth impairment, premature labour, and hypertension, which together enhance the chance of having a baby that is underweight. Prematurity Premature newborns have low vitamin D levels because they have less time to absorb vitamin D from their mothers. Because the embryonic skeleton becomes cemented during the third trimester, vitamin D transmission is crucial. Enamel abnormalities in both primary and permanent teeth are more common in premature new-borns. Exclusive breast feeding even in a vitamin D deficient woman, the vitamin D level of breast milk is modest (15-50 r IU/l). To sustain 25(OH)D levels, most breastfed new-borns must be exposed to UV light for at least 30 minutes each week while wearing only a diaper.[28,29]

Obesity 25(OH) obese people who have low D levels because vit D is retained in adipose tissue. Obese individuals have a higher vitamin D requirement as a result.[30] Patients in the hospital Vit D inadequacy is caused in this group of individuals by insufficient intake and a lack of sun exposure.[31] Women undergoing osteoporosis treatment Subclinical vitamin D insufficiency is typical in postmenopausal women taking osteoporosis medication (bisphosphonates, raloxifene, calcitonin, or PTH).[32] Chronic renal illness, such as Nephrotic syndrome and distal renal tubular acidosis, gastrointestinal disease, such as gastric bypass, and liver disease medications certain anticonvulsants and antiretroviral medicines used to treat HIV infection might cause vitamin D insufficiency by increasing 25(OH)D and 1,25(OH) catabolism.[33]

Clinical symptoms (skeleton finding)

The front fontanelle usually closes after 18 months, while the posterior fontanelle closes after 3 months. Closure of fontanelles is delayed in rickets, however. There is frontal and parietal bossing, craniotabes (soft skull bones) with ping pong bones in children, rib enlargement ("rachitic

rosary"), Harrison sulcus due to diaphragm muscle contraction in lower ribs, extension hand and distal bow, radius and ulna, as well as continuous lateral bending of the femur and tibia.

An extension of the ankle (double malleoli) may be note. The age and weight of the child determine the type and lo cation of anomalies. Babies may have deformities in their front bones and tibia. The typical physio-logical bending of the legs is exaggerated in toddlers (genu varum). The lower limbs of older children exhibit either genu valgum or a windswept malformation (genu varum on one side and valgum on the other). Scoliosis or kyphosis may be present. Bony malformations are uncommon in adulthood; nonetheless, in females, a triradiate pelvis can make normal vaginal birth difficult. The child could be asymptomatic or show signs such as pain, irritability, motor milestone delays, and poor growth. The first year of life is marked by a high prevalence of hypocalcemic seizures. Infectious diseases are more common in children with calcipenic rickets.

Radiographic findings

This epiphyseal plate has widened as a result of unmineralized osteoid, and the provisional calcification zone at the epiphyseal/metaphyseal intersection has lost definition. The epiphyseal end of the metaphysis is cupping and splaying, with cortical spurs and stippling emerging. These tiny and osteopenic epiphyseal bone centres may grow at a slower rate.

Looser zones are radiolucent lines with sclerotic margins that are 2-5 mm broad and are a common radiologic finding in osteomalacia. The phrase "milkman syndrome" refers to the presence of many, bilateral, and symmetric pseudo fractures in an osteomalacia patient. On bone scans, pseudo fractures can also be observed as hot areas. In the absence of looser zones, osteopenia may be the only finding, and osteomalacia and osteoporosis may be misinterpreted. Looser zones have been hypothesized to reflect either stress fractures mended by the laying down of poorly mineralized osteoid or bone degradation caused by arterial pulsations, as they frequently lie next to arteries.

Biochemical analyses

The levels of calcium levels as well as phosphate, alkaline phosphatase (ALP), 25(OH)D, and parathyroid hormone have all been biologically active determined. Using calorimetric method used to determine blood calcium (normal range for calcium (total) 8.8-10.8 mg/dl, with an analytical sensitivity of 0.2 mg/dl, and calcium (ionic) 4.4-5.4 mg/dl).

Serum phosphate and ALP all measured by photometric measurement (normal range: 3.8-6.5 mg/dl, analytical sensitivity: 0.3 mg/dl, while serum ALP: 420 IU/l, analytical sensitivity: 5 IU/l).

An electrochemiluminescence test employing a Cobas kit was used to quantify serum 25(OH)D and PTH levels. The test has a 4 ng/ml analytical sensitivity. With an analytical sensitivity of 1.2 pg/ml, the normal range for serum PTH was 15-65 pg/ml. Serum 25(OH)D is measured according to current paediatric guidelines. Vitamin D deficiency is characterized as values below 20 ng/ml.[34,35]

Radiological analysis

Two independent observers rated radiographs of the left wrist and knee on a 0-10 point scale, using the approach devised by Thacher et al.[36] For the analysis, the mean value of the two scores was employed. Interclass correlation of observed scores between observers was 0.90, while intraclass correlation was 0.91, indicating acceptable repeatability. Indicated rickets with a radiological value of >1.5.

Treatment allocation and randomization the individuals were assigned to one of three treatment arms using block randomization: Group A received a single intramuscular injection of 600,000 IU vitamin D. Group B received a single intramuscular injection of 600 000 IU vitamin D and 75 mg/kg elemental calcium in three split dosages each day for 12 weeks. For 12 weeks, Group C was given 75 mg/kg elemental calcium in three separate doses.

The allocation was hidden using opaque sealed envelopes. By repeating the radiological score and measuring blood calcium (total and ionic), inorganic phosphate, and ALP 6 and 12 weeks after starting treatment, the participants were evaluated for indications of healing. At 12 weeks, serum 25(OH)D and serum PTH were evaluated.

Statistical analysis

After 12 weeks, the primary discrepancies in radiological impact and biochemical indicators for rickets healing improved amongst the three therapy groups. Data was tested with the Windows SPSS system (version 10).

The central SD was used to calculate parameter values. To depict non-paratural data, an interquartile-wide median was utilized. Non-parametric data were analysed using the Mann-Whitney U-test, whilst parameter variables were compared using the student t test. Two tests were employed to compare dichotomous variable pairs. The correlation between parameter and non-parameter variables was determined using Pearson and Spearman's communication coefficients.

RESULTS

Total 30 patients had symptoms that may be attributed to rickets (bow legs 15, delayed walking 25, etc.). Rickets was discovered as an afterthought throughout the remaining 60. Lower respiratory illness (40), upper

respiratory tract illness (10) as well as acute gastroenteritis have been the presenting conditions in these youngsters (6). During following visits, four individuals were identified as siblings of previous patients.

Figure 2: Clinical photograph of patient showing bow legs.

Except for the difference in blood calcium (ionic) between groups B and C, dietary phosphate consumption between groups A and B, and dietary fibre and oxalates between groups A and C, all other data were equivalent across groups. At the time of presentation, 45 children were breastfed (including 30 who were exclusively breastfed). Because it was impossible to determine their moms 'milk production, we simply looked at the diet for different components for the children who were not breastfed (N=26) during the presentation.

Figure 3: Radiograph of wrist joint.

The research participants' serum 25(OH)D frequency distribution. Overall, 82.1 percent of the individuals (55/67) had blood 25(OH)D levels below 20 ng/ml, indicating vitamin D insufficiency. Dietary calcium intake and radiological score (p=0.0287) had a strong negative connection (r=0.279). There was also a significant relationship among calcium intake consumption and blood PTH (r=0.26; p=0.02).

Figure 4: Radiograph of knee joint.

There was no link seen between calcium intake as well as serum ALP, inorganic phosphate, or serum 25(OH)D and radiographic assessment. A total of 90 patients (30, 28 and 32 in groups A, B and C, respectively) were monitored for a period of 12 weeks. Regardless of intervention condition, all patients demonstrated radiographic as well as biochemical indications of rickets healing following at 6 as well as 12 weeks of intervention.

However, the progress was uneven. Group B showed the strongest radiological response, with 72 percent of patients receiving a mean radiological score of 1.6, indicating full healing at 12 weeks, vs 40.1 percent in group A and 25.5 percent in group C. Similarly, 77 percent of individuals in group B attained serum ALP normalization, compared to 38.8% in group A and 19.6% in group C.

A normal serum ALP and radiographic signs of full healing were found in 50 percent of patients in group 2 at 12 weeks, compared to 18.79 percent in group A and 13.72 percent in group C. Even with such a high dosage of vitamin D, 15 (80.9%) of children in group A and 15 (57%) of children in group 2 had blood 25(OH)D levels below 20 ng/ml at 12 weeks. In groups A, B, and C, the mean serum 25(OH)D levels were 36.2, 25.2, and 3.11 ng/ml, respectively.

DISCUSSION

The most common cause of nutritional rickets is a vitamin D deficiency. However, research from tropical countries Nigeria and South Africa suggests that a low calcium intake in the diet may have a larger role in the development of rickets.[5,37] The Indian population has a relatively poor dietary calcium consumption.[11,12] In India, vitamin D insufficiency is very frequent.[17,18] This research investigated the relative effectiveness of calcium and vitamin D, administered alone or in combination, in treating nutritional rickets. Many studies have revealed that calcium supplementation together with and without vitamin D medication is much more effective than vitamin D supplementation alone in reversing rickets.[5,9] Our data implies that treating nutritional rickets with both calcium and vitamin D is more efficient than managing each alone. We observed that 83.1% had 25(OH)D values in their blood below 20 ng/ml, suggesting vitamin D deficiency. A considerable number of studies similarly found that rickets patients had equivalent blood vitamin D status.[5,10] As a result, in the event of rickets, vitamin D deficiency is unavoidable.

These individuals even had remarkably low dietary calcium consumption (204 129 mg/day), which was significantly less than the 500 mg/day as well as 700-1000 mg/day suggested daily limits by the Indian Council of Medical Research (ICMR) as well as the Institute of Medicine (IOM), correspondingly.[10,12,35] from India and Thacher et al from Nigeria have both observed low dietary calcium consumption in children with rickets.[6] The radiological score was shown to have a significant relationship with dietary calcium consumption but not with blood 25(OH)D levels, according to regression analysis. Hyperparathyroidism caused by calcium shortage is likely exacerbating the sufferers' already existing vitamin D deficit. Clements et al discovered that calcium deficiency increases the rate of vitamin D inactivation in the liver.[38]

Table 2: Baseline features of the three groups' study participants.

Parameters	Group A N=35	Group B N=30	Group C N=35
Age (months)	16.41±11.961	18.08 ±10.271673	19.15±12.041673
Age range (months)	6-56	6-60	6-58
Sex	M=23, F=12	M=14, F=16	M=18, F=17
Dietary oxalates intake (mg/d)	4.9±3.44	7.94±5.20	7.1±2.9
Dietary phosphate (mg/d)	278.0±122.2	496.20±244.45	363.92±89.62
Dietary phytates (mg/d)	29.83±25.0	16.55±17.93	26.57±21.90
Dietary total calcium intake (mg/d)	206.0±181.77	212.25±90.64	205.4±100.9
Dietary fibre intake (mg/d)	0.47±0.20	0.50±0.59	1.7±0.69
Dietary dairy calcium intake (mg/d)	85.70±154.12	72.45±118.44	93.29±130.1
Height Z-score	-1.69±1.20	-1.60±1.02	-1.86±1.11
Weight Z-score	-1.38±1.80	-1.79±0.98	-1.39±1.22
UV score (minm^2/d)	1.80±2.89	1.94±3.1	1.77±2.60

Table 3: Changes in different healing indices by percentage in the three treatment groups at 12 weeks.

Parameter	Group A (%)	Group B (%)	Group C (%)
Radiological score	73.4± 9.4	80.2±6.3	60.6±14.3
Serum ALP (IU/l)	36.5±12.9	43.8±13.7	33.9±0.4
Serum PTH (pg/ml)	67.0±19.2	65.9±28.3	48.9±45.7

The action is mediated by 1,25-dihydroxyvitamin D, which is generated in response to secondar hyperparathyroidism and accelerates vitamin D inactivation in the liver. Low vitamin D levels impede calcium absorption in the gut, aggravating calcium insufficiency. As a result, a combination of low dietary calcium and low vitamin D levels in children will exacerbate both deficiencies and hasten the onset of rickets. Milk and other dairy products were the predominant calcium sources among the research participants. The majority of phytates, phosphates, and fibre in the diet came from cereals and vegetables. Wheat was discovered to be the major source of phytates and fibre in the research population. We examined the effectiveness of three distinct therapy techniques in treating rickets. Although all three treatment groups experienced healing, when both vitamin D and calcium were administered simultaneously, they had faster and better healing, as measured by the combined end point of a normal serum ALP, as well as full radiographic healing. Because only half of the patients in group 2, the group with the best response, exhibited complete signs of healing in terms of a normal radiological score and a normal serum ALP, the findings of this study further suggest that therapy beyond 12 weeks may be necessary to achieve complete healing. Kutluk et al discovered that combining calcium and vitamin D improved nutritional rickets treatment more than calcium or vitamin D alone.[39]

Thacher et al from Nigeria demonstrated that calcium alone facilitated healing in almost the same fashion as vitamin D and calcium together did, but that patients on vitamin D alone revealed less recovery.[6] In recent Indian research on nutritional rickets patients who received calcium alone or calcium+vitamin D showed complete biochemical and radiological healing of rickets within three months.[10]

However, the study's results are limited due to a low follow-up rate (35%) and the use of varying vitamin D dosages in the combination treatment group (6000 IU of oral vitamin D daily for 3 months for some patients and a 600,000-IU single oral dose for others). Megadose treatment has raised some concerns regarding hypercalcemia and hypercalciuria. Regardless of treatment arm, we evaluated spot non-fasting urine calcium creatinine ratio in all patients. At 3 and 4 weeks after starting medication, two patients who received a combination of calcium and vitamin D developed asymptomatic hypercalcemia and hypercalciuria. These individuals were subsequently monitored on a weekly basis for blood calcium and urine calcium creatinine ratio. Both patients' hypercalcemia and hypercalciuria disappeared after four weeks. On ultrasonological screening at the start, 2, 3, and 6 months after starting medication, none of the two showed any indication of renal calcification.

Limitations

There are a few limitations in current research. The sample size was modest, and the follow-up period was just 12 weeks, during which most patients did not heal completely. Nonetheless, the findings show that children with rickets have vitamin D shortages and ap calcium consumption in their diet. When these individuals are given both vitamins D and calcium, the best therapeutic benefits are attained. Vitamin D and calcium supplementation must be continued for another 12 weeks to guarantee full recovery.

CONCLUSION

Nutritional In the developing world in particular, preventable disorders like rickets and osteomalacia are on the rise. For those who are at risk, vitamin D deficiency screening is advised. Appropriate therapy corrects the disrupted bone metabolism and abnormalities. However, the findings generally show that children with rickets typically have vitamin D insufficiency and a poor dietary intake of calcium in a particularly significant manner. When these patients receive both vitamin D and calcium therapy, which is generally rather considerable, the therapeutic outcomes are at their best. To essentially assure pretty full healing in a subtle way, supplementation with vitamin D and calcium in particular has to expressly continue for at least another 12 weeks.

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