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Original Research Article

Management of Nutritional Rickets in Indian Children: A Randomized Controlled Trial

Herschel Dafal[1], Santosh Mishra[2], Kishor Uikey[3], Swati Saral[4*]

[1]Associate Professor, Department of Community Medicine, LNMCH, Indore, MP, India
[2]Assistant Professor, Department of Orthopedics, GMC Bhopal, MP, India
[3]Assistant Professor, Department of Orthopedics, CIMS, Chhindwara, MP, India
[4]Assistant Professor, Department of Pediatrics, Ram Krishna Medical College, Bhopal, MP, India

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Corresponding Author: Dr. Swati Saral
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Abstract:

Background: A prominent cause of rickets is a deficiency in vitamin D. Recent researches have suggested that a lack of dietary calcium may be a contributing factor to its cause. The relative efficacy of calcium, vitamin D, or a combination of them in treating rickets is not well-established.

Objective: To ascertain the effect of vitamin D therapy, calcium therapy, or a combination of the two on the nutritional rickets healing process in young children.

Material and Methods: A randomized controlled experiment with 67 patients with nutritional rickets, ages ranging from six months to five years, was conducted. For a period of 12 weeks, they were randomized to receive either calcium (75 mg/kg/day elemental calcium orally), vitamin D (600000 IU single intramuscular injection), or a combination of the two. Each person's demographic information, nutritional status, calcium intake from food, and phytate intake were assessed. In order to measure the degree of healing, baseline, 6-week, and 12-week radiographs of the wrist and knee as well as biochemical markers such as blood calcium, inorganic phosphate, alkaline phosphatase, 25-hydroxycholecalciferol, and parathyroid hormone were evaluated.

Results: The average daily intake of calcium from food was 204.01 ± 129.01 mg, which was inadequate in every case. The mean serum 25-hydroxycholecalciferol D level was 15.91 ± 12.41 ng/ml. Serum vitamin D levels below 20ng/ml were found in 82.1% of the patients, suggesting a deficiency in vitamin D. After 6 and 12 weeks of treatment, all therapy groups showed some degree of radiological and biochemical signs of curing rickets, but to different degrees. Compared to 15.7% on vitamin D alone and 11.7% on calcium alone, 50% of patients on combination therapy attained the integrated end objective of normal blood alkaline phosphatase and complete radiographic healing at 12 weeks.

Conclusion: Children who developed rickets had lower dietary calcium intake and a blood vitamin D deficit. The most effective treatment outcome was shown when vitamin D and calcium were combined, rather than when each was administered alone.

Keywords: Calcium; Nutritional rickets; vitamin D.

Introduction

A common nutritional problem called rickets is usually brought on by a deficiency in vitamin D. According to recent studies conducted in tropical countries, rickets may be significantly influenced by calcium deficiency. [1-6] In Nigerian children with rickets, calcium treatment alone was just as effective at promoting recovery as a calcium and vitamin D combination. [1]

Adult and pediatric studies in India [7, 8] have shown that our population's calcium intake is substantially below the recommended range. Indian cuisine mostly consists of grains and lentils, is mostly vegetarian, and usually excludes dairy and dairy products. [9] The increased phytate levels in the vegetarian meals exacerbate the diet's low calcium content. Research from a number of nations, including India, has shown that vitamin D deficiency is rather common. [10–13]

In a recent study, Seth et al. [14] found that blood 25-hydroxycholecalciferol D (25-OHD) levels were below 10ng/ml in 47.8% of healthy breastfeeding mothers and 43.2% of their newborn kids.

The significance of calcium and vitamin D shortages to the development of rickets in children in India and other Asian nations is unclear, making it difficult to determine the best treatment plan.

Aim and Objectives:

Our goal was to find out the impact of calcium, vitamin D, or a combination of the two supplements affected Indian children's ability to recover from nutritional rickets.

Material and Methods:

We included 100 consecutive children from the outpatient department of a tertiary care teaching hospital in Central India, ranging in age from 6 months to 5 years, who had clinical and radiological symptoms of nutritional rickets. Individuals with symptoms suggesting non-dietary reasons (liver or renal disease, malabsorption issues, anti-epileptic medication use, or any chronic condition) were excluded from the research. Additionally, those who experienced hypocalcemic seizures or had taken supplements containing calcium or vitamin D during the previous six months were not allowed. When necessary, appropriate laboratory testing was done to rule out non-nutritional rickets. The parent or legal guardian of each kid gave informed written consent, and participation was voluntary. The institutional ethics committee gave its approval to the study protocol. Of the 100 children assessed, 18 had used calcium or vitamin D supplements within the previous six months, 5 had a long-term medical or surgical condition, 7 were older than appropriate, and 3 had not given their permission. In all, 67 instances were included in the study. [Figure 1]

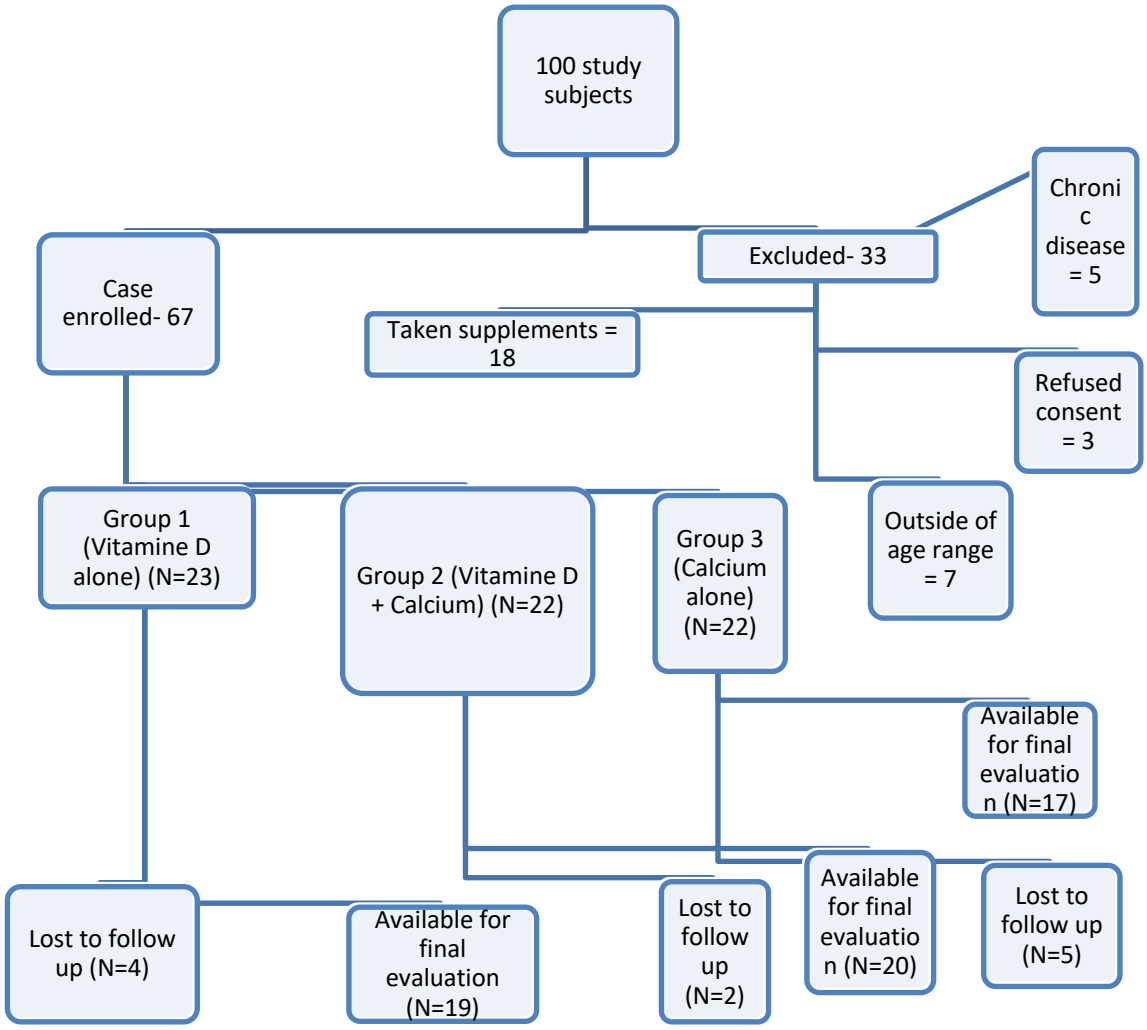

Figure 1: Study flow chart

Data and sample collection:

The demographic characteristics of the selected individuals, such as age, gender, and monthly family income, were evaluated. A thorough nutritional evaluation was carried out, which includes the introduction of additional meals and a review of breastfeeding. Dietary assessment was performed to ascertain the consumption of calcium, phosphates, and phytates from dairy products using a food frequency questionnaire and a 24-hour dietary recall.

Additionally, specifics on the nature, timing, and length of the symptoms were sought. Weight and height measurements were made, and Z-scores for

height and weight in relation to age were calculated using the World Health Organization's 2006 growth reference standards. For children under two years old, measurements of length were also obtained. [15].

Biochemical measurements:

The biochemical test measured the levels of serum calcium, phosphate, alkaline phosphatase (ALP), 25-OHD, and parathyroid hormone (PTH). Serum calcium levels were determined using a calorimetric technique. The normal range for total calcium is 8.8–10.8 mg/dl with an analytical sensitivity of 0.2 mg/dl, and for ionic calci-um, it is 4.4–5.4 mg/dl. Serum phosphate and ALP levels were measured using photometric analysis.

Serum ALP had a normal range of 420 IU/l and an analytical sensitivity of 5 IU/l, whereas serum phosphate had a normal range of 3.8–6.5 mg/dl with an analytical sensitivity of 0.3 mg/dl. Utilizing a Cobas kit for electrochemiluminescence testing, the levels of PTH and serum 25OHD were determined. The analytical sensitivity of the test was 4ng/ml. Serum PTH had a standard range of 15–65 pg/ml and an analytical sensitivity of 1.2 pg/ml. Current pediatric guidelines state that serum 25OHD values less than 20ng/ml are suggestive of vitamin D deficiency. [16,17]

Radiological evaluation:

Using a 0–10 point rating system, two observer's evaluated radiographs of the left wrist and knee utilizing the Thacher et al. approach. For the purposes of the study, the mean of the two scores was used.

Excellent repeatability was demonstrated by the intraclass correlation coefficient of ≥0.91 and the interclass correlation coefficient of 0.90 between the ratings of the observers. A radiological score of more than 1.5 was indicative of rick-ets.

Randomization and treatment allocation:

Block randomization was used to randomly assign the participants to one of three treatment groups:

- Group 1: One intramuscular injection of 600 000 IU of vitamin D.
- Group 2 received a single intramuscular injec-tion of 600 000 IU of vitamin D and three split daily dos-es of 75 mg/kg of elemental calcium for a duration of 12 weeks.
- Group 3: Three split daily dosages of 75 mg/kg elemental calcium for a period of 12 weeks.

Effectively packaged opaque envelopes were utilized to hide allocations. To track the patients' healing progress, follow-up evaluations were conducted six and twelve weeks following the commencement of therapy. This was accomplished by taking new measurements of the radiological score, blood calcium (total and ionic), inorganic phosphate, and ALP. After 12 weeks, serum PTH and serum 25-OHD were assessed again. The treatment regi-men were unknown to the scientist and the radiologist.

Statistical analysis:

After 12 weeks, the biochemical markers of rickets recovery and the improvement in radiological score were the primary features that were compared across the three therapy groups. Version 10 of the Windows SPSS software was used to analyze the data.

The mean ± standard deviation was used to show the parametric data. The interquartile range was displayed with the median for non-parametric data. Student's t-test was used to analyze parametric data, while Mann-Whitney U-test was used to analyze non-parametric variables. The chi-square test was utilized to analyze binary data. The Spearman correlation coefficient was used for non-parametric variables while the Pearson correlation coefficient was used to examine the link between parametric variables.

Results:

Out of the patients, 20 showed symptoms mostly related to rickets, such as bow legs in 14 instances and delayed walking in 14 cases. Rickets was incidentally discovered in the remaining 47 cases. Acute gastroenteritis (2 cases), URTI (6 cases), LRTI (37 cases) and acute gastroenteritis (2 cases) were the diagnoses made on the children.

On further trips, two of the people were the siblings of patients who had been contacted before. Table 1 shows the patients' baseline characteristics. With the exception of differences in blood calcium (ionic) levels among groups 2 & 3, dietary phosphate consumption among groups 1 and 2, and dietary fibre and oxalates between groups 1 and 3, all results were identical between the groups. When they arrived, forty-one children had been nursed, thirty of them just once. We assessed the diet of just those 26 children who were not breastfed at the time since it was impractical to de-termine the milk supply of their moms.

Table 1: Baseline variables

Parameter	Group 1 (N = 23)	Group 2 (N = 22)	Group 3 (N = 22)	P (1 vs. 2)	P (2 vs. 3)	P (3 vs. 1)
Age (months)	16.49 ± 11.97	17.06 ± 10.68	19.28 ± 13.05	0.981	0.541	0.461
Age range (months)	6-58	6-60	6-60	-	-	-

Gender	M=13, F=10	M=9, F=13	M=13, F=9	-	-	-
Height Z-score	-1.721 ± 1.01	-1.591 ± 1.07	-1.821 ± 1.18	0.661	0.491	0.751
Weight Z-score	-1.391 ± 1.11	-1.771 ± 0.97	-1.341 ± 1.13	0.231	0.181	0.871
UV score (min·m^2/d)	1.781 ± 2.83	1.961 ± 3.1	1.741 ± 2.71	0.831	0.831	0.961
Dietary total calcium intake (mg/d)	204.01 ± 182.68	202.26 ± 91.67	207.41 ± 100.21	0.981	0.911	0.891
Dietary dairy calcium intake (mg/d)	88.71 ± 156.03	73.56 ± 112.78	94.28 ± 124.41	0.981	0.571	0.951
Dietary fiber intake (mg/d)	0.42 ± 0.31	0.56 ± 0.55	1.11 ± 0.68	0.491	0.081	0.011(S)
Dietary phosphate (mg/d)	274.01 ± 132.21	490.28 ± 249.46	360.98 ± 86.68	0.031 (S)	0.141	0.101
Dietary phytates (mg/d)	29.84 ± 25.01	16.56 ± 17.94	26.58 ± 21.91	0.231	0.313	0.751
Dietary oxalates intake (mg/d)	4.71 ± 3.95	7.85 ± 5.01	7.81 ± 2.41	0.161	0.161	0.041(S)

S- Significant

The frequency distribution of serum 25-OHD amongst study participants is shown in Figure 2. Overall, 82.1% of the individuals (55 out of 67) had blood 25OHD levels below 20ng/ml, indicating a deficit in vitamin D. There was a notable inverse relationship between the amount of calcium consumed through food and the radiological score, with a p-value of 0.0288. There was a significant connection between dietary calcium consumption and blood PTH (p = 0.021).

No correlation was seen between the amount of calcium consumed through diet and the levels of serum ALP as well as inorganic phosphate, or between the levels of serum 25-OHD and radiological score.

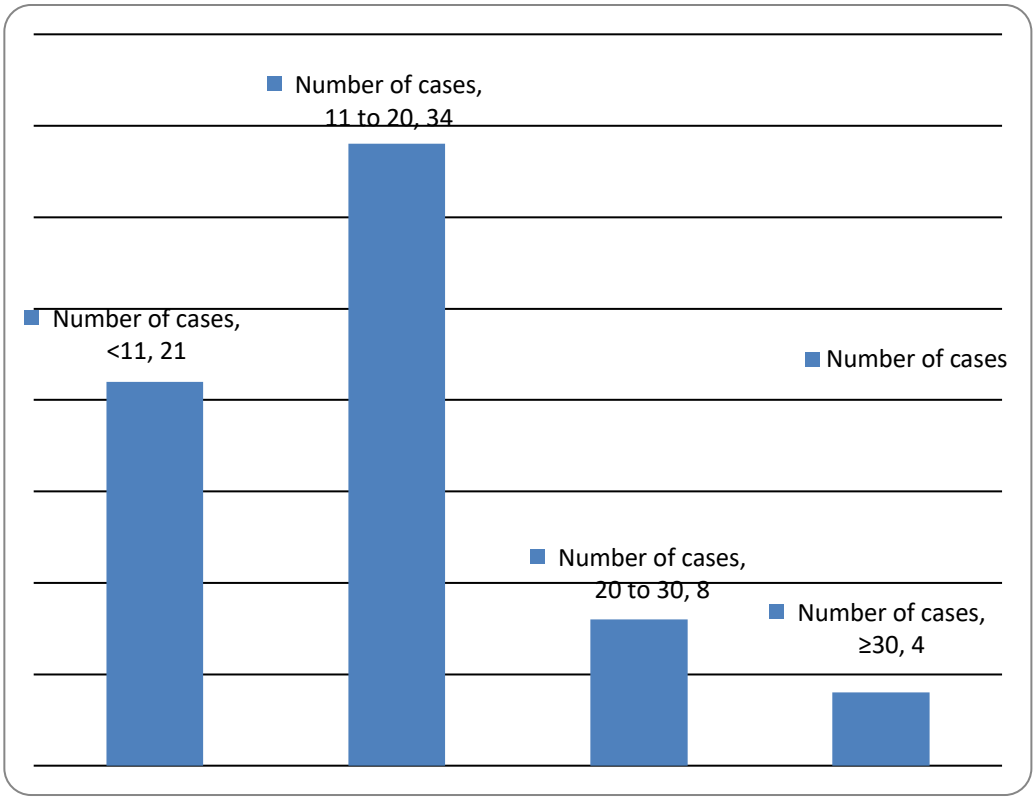

Figure 2: Frequency distribution of serum 25-OHD levels in study participants

There were 56 patients in all, including 19 in group 1, 20 in group 2, and 17 in group 3, who were monitored for 12 weeks. After six and twelve weeks of treatment, every single patient, irrespective of the therapy group, showed radiological and biochemical evidence of the rickets healing. The degree of improvement varied, as Tables 2 and 3 demonstrate. In comparison with 42.1% in group 1 and 23.5% in group 3, group 2 had the strongest radiological response, with 70% of patients displaying a mean radiological score of ≤1.5, suggesting complete healing at 12 weeks. Serum ALP normalization was attained by 70% of patients in group 2, compared with 36.8% in group

1 & 17.6% in group 3. In comparison with 15.7% in group 1 & 11.7% in group 3, 50% of the participants in group 2 had comparable blood ALP levels & radiographic evidence of complete healing at 12 weeks.

Table 2: Effect of treatment with vitamin D alone (group 1), combination of vitamin D and calcium (group 2) and calcium alone (group 3) on parameters of healing

Parameter		Group 1 (N = 19)	Group 2 (N = 20)	Group 3 (N = 17)	P (1 vs. 2)	P (2 vs. 3)	P (3 vs. 1)
Serum Alkaline Phosphatase (IU/L)	Baseline	1222.41 ± 325.41	1404.51 ± 381.51	1212.81 ± 290.81	0.091	0.071	0.911
	12 weeks	539.31 ± 208.11	363.81 ± 135.71	535.61 ± 169.71	0.011	0.011	0.881
Serum Phosphate (mg/dl)	Baseline	2.81 ± 0.71	2.61 ± 0.61	2.91 ± 0.81	0.391	0.281	0.811
	12 weeks	4.71 ± 0.51	5.31 ± 0.51	4.41 ± 0.61	0.011	0.011	0.441
Serum 25-OHD (ng/ml)	Baseline	14.11 ± 10.51	19.41 ± 17.91	14.41 ± 5.71	0.231	0.221	0.881
	12 weeks	32.81 ± 23.81	31.01 ± 30.91	21.41 ± 21.71	0.061	0.921	0.071
Serum PTH (pg/ml)	Baseline	170.11 ± 108.11	228.51 ± 216.67	137.41 ± 98.91	0.261	0.081	0.291
	12 weeks	51.51 ± 33.41	45.91 ± 40.11	48.61 ± 34.71	0.651	0.191	0.091
Total Serum Calcium (mg/dl)	Baseline	8.61 ± 0.91	8.41 ± 0.81	8.71 ± 0.71	0.321	0.321	0.771
	12 weeks	9.51 ± 0.61	10.31 ± 0.81	9.51 ± 0.61	0.011	0.011	0.481
Ionic Serum Calcium (mg/dl)	Baseline	3.91 ± 0.51	3.71 ± 0.31	4.01 ± 0.61	0.081	0.031	0.591
	12 weeks	4.71 ± 0.41	5.11 ± 0.51	4.71 ± 0.31	0.011	0.011	0.111
Radiological Score	Baseline	7.51 ± 2.91	8.51 ± 2.11	7.81 ± 2.21	0.231	0.451	0.671
	12 weeks	2.11 ± 0.71	1.41 ± 0.41	3.31 ± 1.71	0.011	0.011	0.011

After 12 weeks, despite taking a high dosage of vitamin D, 11 out of 20 children in group 2 (55%) and 15 out of 19 children within group 1 (78.9%) still had low blood 25-OHD levels (<20 ng/ml). Groups 1 and 2 had average serum 25-OHD levels of 32.81±23.81 & 31.01±31.01 ng/ml, respectively.

Table 3: Percentage change in various parameters of healing at 12 weeks in the three treatment groups

Parameters	Group 1	Group 2	Group 3
Serum ALP (IU/L)	34.51 ± 13.81	42.91 ± 12.31	34.21 ± 0.21
Serum PTH (pg/ml)	69.01 ± 18.11	65.61 ± 28.81	49.71 ± 46.01
Radiological Score	70.41 ± 9.31	82.21 ± 5.81	59.61 ± 15.81

Discussion:

A vitamin D deficiency is frequently linked to nutritional rickets. Research from tropical countries such as South Africa [19] and Nigeria [1] has shown that rickets may be significantly caused by a diet low in calcium. Dietary calcium consumption is quite low in the Indian population [7, 8]. Children in India are often deficient in vitamin D [13, 14].

This study looked at how well calcium and vitamin D worked alone or in combination to cure nutritional rickets. In order to promote recovery from rickets, calcium supplementation—whether taken in conjunction with or without vitamin D treatment—proves to be more advantageous than vitamin D supplements alone, according to several studies [1–5]. Our results suggest that when calcium and vitamin D are administered together, nutritional rickets patients recover more quickly than when they get these treatments separately.

82.1% of the subjects had blood 25OHD levels < 20 ng/ml, which is indicative of a vitamin D deficiency. Comparable values of blood vitamin D have been seen in rickets sufferers in other research [2, 6]. In cases of rickets, vitamin D deficiency is always present. In this investigation, we found that patients' average daily calcium consumption was a considerably low 204.01 ± 129.01 mg. This quantity is much less than the 500 mg daily intake suggested by the Indian Council of Medical Research (ICMR) [8] and the 700–1000 mg daily dosage suggested by the Institute of Medicine (IOM). [20] Both Thacher et al. [2] and Balasubramanian et al. [6] from Nigeria and India have shown decreased dietary calcium consumption in rickety children. A regression analysis showed that, whereas blood 25-OHD levels were not significantly correlated with radiological score, dietary calcium consumption was.

There's a good chance that the individuals' hyperparathyroidism from low calcium exacerbates

their vitamin D deficiency. In animal experiments, it was demonstrated by Clements et al. [21] that a calcium shortage accelerates the pace at which vitamin D inactivates in the liver. The effect is aided by 1,25-dihydroxyvitamin D produced as a result of secondary hyperparathyroidism, which triggers the liver's conversion of vitamin D into polar, inert compounds. Calcium deficiency is made worse by low vitamin D, which inhibits the gut's ability to absorb calcium. As a result, low calcium intake and low vitamin D levels will aggravate deficiencies and cause rickets to develop in children. The research population's main sources of calcium were milk along with other dairy products. Grains and vegetables were the primary dietary sources of fiber, phosphates, and phytates. In the population under investigation, wheat serves as the primary food source and has been found to be the main source of fiber and phytates.

To find out how well three therapy approaches worked for curing rickets, we assessed them. Full radiographic healing in each of the treatment groups and normal blood ALP levels indicate that joint vitamin D and calcium administration led to more effective healing more quickly than either treatment alone. According to the study, extended therapy beyond 12 weeks is essential for complete healing, even though only half of the patients in group 2, which had the greatest response, showed complete evidence of healing with normal radiographic scores as well as serum ALP levels.

When treating nutritional rickets, Kutluk et al. [22] from Italy found that taking calcium and vitamin D supplements together had a better outcome than taking either vitamin D or calcium supplements alone. Researchers Thacher et al. [1] found that calcium therapy alone produced a similar level of recovery as calcium plus vitamin D therapy.

Nevertheless, fewer individuals who were given simply vitamin D exhibited healing symptoms. Patients who administered calcium alone or calcium with vitamin D had complete biochemical and radiological recovery of rickets after three months, according to a previous study on nutritional rickets in India [6]. However, the poor follow-up rate of 40% and the different vitamin D doses utilised in the combination therapy group—6000 IU of oral vitamin D daily for three months for some patients, and a single oral dose of 600,000 IU for others—limit the interpretation of the study's findings.

Concerns have been raised regarding hypercalcemia and hypercalciuria brought on by megadose therapy. Regardless of the treatment group, we measured the calcium creatinine ratio in the spot non-fasting urine of every patient. Three to four weeks after beginning treatment, two people who received a combination of calcium and vitamin D experienced asymptomatic hypercalcemia and hypercalciuria. These people were then followed up with weekly blood calcium checks and urine calcium creatinine ratio measurements. After four weeks, the hypercalcemia and hypercalciuria in both individuals resolved. When the two patients were evaluated by ultrasonography at the beginning, 2, 3, and 6 months into their therapy, none of them had any symptoms of renal calcification. The data was insufficient to reach any conclusions on safety issues, and the research did not concentrate on toxicity.

Limitations of the study:

We would want to draw attention to our study's shortcomings. With a small sample size and a short follow-up time of 12 weeks, the majority of cases did not fully recover.

Conclusion

The results indicate that children with rickets had low dietary calcium intake and insufficient vitamin D. When these patients receive therapy with both calcium and vitamin D, the best possible results are obtained from their therapies. For a complete recovery, vitamin D and calcium supplements must be taken for an additional 12 weeks.

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