ORIGINAL ARTICLE

Treatment Outcome of Oral Versus Injectable Vitamin D in Nutritional Rickets in Children

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ABSTRACT

Background: Rickets is a disease of growing bones which occurs before fusion of epiphyses. It is defined as failure of mineralization of growing bone or osteoid tissue. Vitamin D comes from two sources sunlight and diet. Treatment of vitamin D deficient rickets includes daily supplementation of vitamin D compared to stoss dose of vitamin D given orally or in injectable form.

Aim: To determine the treatment outcome of oral (mega dose or daily vitamin D) versus injectable mega dose in the treatment of nutritional rickets in children.

Method: This Randomized controlled trial was conducted atDepartment of Pediatric Medicine Mayo Hospital, Lahore from Jan 2015 to Jan 2017.Total 198 patients fulfilled the criteria were selected. All children were allocated into 3 groups, A, B & C. Treatment allocation was done using Lottery method. Group-A received oral mega dose of vitamin in a dose of 200,000 units, Group-B received injectable vitamin D in form of 200,000 units and Group-C was given vitamin D daily, 5000 units if age less than one year and 6000 units if more than one year for 30 days. All the children were followed up for two more visits at day 30 & 90. Clinical, biochemical & radiological data obtained at admission and follow-up was recorded.

Results: The average age of patients was 13.22 ± 8.21 months with 121(61%) male and 77(39%) female cases in this study. At 3rd month the weight gain was highest in group-B (1.09±0.55kg), followed by group-A (0.635±0.28kg) then group-C (0.36±0.31kg). This was statistically significant p-value < 0.0001. Mean calcium level at 3rd month in group-B was 9.04±0.33 mg/dl while the mean calcium level in group A & C, were 8.81±0.29 and 8.83±0.34 mg/dl respectively, with significantly higher levels in group B in comparison to group A & group C, p-value < 0.001. The mean phosphate levels remained same in all three groups at each visit, p-value > 0.05. At 3rd month the mean Vitamin D levels were significantly higher in group B in comparison to group A & group C, p-value < 0.005 while group-A and group-C had statistically comparable Vitamin D levels, p-value > 0.05. The mean Thacher Score at last visit was 0.28±1.25 in group-A, 0.48±1.34 in group-B and 0.81±1.55 in group-C,

Conclusion: Through the findings of this study, it is concluded that radiological healing was equal in injectable and oral groups. Vitamin D level was higher in injectable group compared to oral group in our study.

Keywords: Children, Rickets, Serum 25(OH)D,Thacher Score

INTRODUCTION

Rickets is a disease of growing bones which occurs before fusion of epiphyses. It is defined as failure of mineralization of growing bone or osteoid tissue. The bones become soft and fragile. Nutritional vitamin D deficient rickets is defined as rickets occurring due to inadequate dietary intake or insufficient cutaneous synthesis of vitamin D and calcium.[1] Nutritional rickets is prevalent in developing regions of the world and ranks among the five most common diseases in children.[2] Although in developed countries it was thought to be vanquished but is emerging again. Prevalence of rickets in South East Asia is 15-18%.[3, 4] Approximately one billion population of the world is suffering from vitamin D deficiency. In studies done in Turkey, Saudi Arabia and other countries, 50% children were found to have 25OH vitamin D level below 20ng/ml[5]. Vitamin D deficiency is defined as having serum levels of 25OH vitamin D below 20ng/ml while vitamin D insufficiency is defined as having serum levels in the range of 21ng/ml to 29ng/ml. Levels above 30ng/ml are sufficient for bone growth[5].

The causes of nutritional rickets include decreased sun exposure, drinking unfortified animal milk, overclothing, delayed weaning, absence of dietary supplementation with vitamin D, dark skin pigment, Indian/South Asian and African ethnicity, age ≤2 years, exclusive breast feeding, and southern latitude, particularly when combined with season (winter/spring), diet high in phytate and phosphate which decreases absorption of dietary calcium[1,6,7]. Exclusive breast feeding with inadequate vitamin D supplementation in mother and baby is a well-known cause of rickets[8,9].

Vitamin D comes from two sources sunlight and diet. The AAP recommends that all children should receive 400IU of vitamin D daily right after birth of the child[10]. Vitamin D synthesis occurs in skin. 7 dehyrdrocholesterol is

Received on 10-12-2019
Accepted on 29-05-2020

converted by sunlight to pre-vitamin D which undergoes isomerizaton to vitamin D and is transported by Vitamin D binding globulin to the liver to undergo another process called 25 hydroxylation. It then goes to the kidney for 1 alpha hydroxylation[11-13].

The clinical features of rickets include proximal myopathy, hypotonia, growth delay, bone pains etc. Physical findings include craniotabes, frontal bossing, waddling gait, widening of wrists and ankles, delay in milestones of development, and enlargement of costochondral junction[9,14-16]. Radiological features of rickets include widening and cupping of metaphyseal region, fraying of metaphysis, frontal bossing and bowing of long bones.[17]

Similarly vitamin D excess has its side effects. These include hypercalcemia, nephrocalcinosis, polyuria, pruritis, nausea, vomiting, constipation and rarely arrhythmias. So it is important that treatment modality corrects the deficiency but does not cause side effects. Treatment of vitamin D deficient rickets includes daily supplementation of vitamin D compared to stoss dose of vitamin D given orally or in injectable form. All the methods have their relevance and benefits. Rickets can be treated by givingdailyvitamin D in dose of 1000 units per day for less than one month old,1000-5000 units per day for 1 -12 months of age and 5000 -10000 units per day for >12 months of age for 4 weeks. Stoss therapy includes giving mega dose of 100,000 to 60,0000 units of vitamin D as injection or in oral form divided over 1-5 days.[18-20] Various studies have been done on giving mega dose of vitamin D. In one study, injectable vitamin D was given in dose of 10,000 units/kg to children with disease and followed for 3 months.[21]Another study showed that one-day treatment with vitamin D was an ideal practice and was also effective. Compliance issues were solved and response was evoked in 4 to 7 days in nutritional rickets. It also helps in distinguishing nutritional rickets from hypophosphatemic rickets[22].

One study compared the effectiveness of vitamin D mega dose in range of 150,000 to 600,000 units. Vitamin D can be given in any dose between this range and resulted in equal and similar healing of rickets. However giving vitamin D in mega dose of 600,000 units has some risk of hypercalcemia.[23] Not a single study has been reported in literature which compares the oral and injectable mega dose of vitamin D to daily therapy for treatment of nutritional rickets[11].

A similar study was done in Pakistan on management of rickets[24]; the oral and injectable route were equally efficacious. The different studies showed that oral and injectable route were equally effective but generally injectable route is believed to be more efficacious because of better absorption and no first pass metabolism in liver.[25] On the other hand, oral route has psychological advantage for mothers because of fear of injection. Thus there is always felt need to compare different methods of vitamin D administration to effectively treat rickets, without untoward effects.

METHODOLOGY

This study was a randomized clinical trial conducted in department of pediatrics Mayo Hospital,Lahore from Jan 2015 to Jan 2017. A letter of ethical permission was taken from Institutional Board Review. Consent was taken in writing from the guardian of the child.198 patients were selected and randomly divided into three groups using Lottery method. The inclusion criteria was children aged six months to three years and having clinical features and x-ray findings of rickets. The clinical features included widening of wrists and ankles,rachitic rosary,frontal bossing, Harrison groove,etc. Radiological features included metaphyseal cupping, fraying, splaying,widening of growth plate, osteopenia. Exclusion criteria was children suffering from rickets other than nutritional type,children presenting with obvious congenital anomalies or suffering from kidney, liver disease, malabsorption or taking drugs like antiepileptics and having already taken Vitamin D mega dose.

Profile of each patient was recorded with respect to age, gender, height, weight and socioeconomic background. Detailed history and clinical examination was done. The history would include milestones of development, duration of sun exposure, nutritional history, and evidence of other diseases. Symptoms and signs of rickets present in each individual child were noted. Baseline labs include CBC, serum Ca, Phosphate, Alkaline phosphatase before start of treatment. 25 OH vitamin D level was done for each child before giving vitamin D and again at day 90 to see improvement in levels. Radiograph of left wrist AP and knee joint AP were taken to look for evidence of rickets. 198 patients were allocated into 3 groups A, B &C. Treatment allocation was done using Lottery method. Group-A received oral mega dose of 200,000 units of vitamin D, Group-B received injectable vitamin D in form of 200,000 units and Group-C was given vitamin D daily, 5000 units if age less than one year and 6000 units if more than one year for 30 days Thacher score was calculated before treatment. All the data obtained was recorded on proforma for analysis.

All the children were followed up for two more visits at day 30 and day 90. Clinical, biochemical and radiological data obtained at admission and follow up was recorded. We looked for normalization of Ca, Phosphate and alkaline phosphatase over 3 months. Improvement in levels of vitamin D was recorded to see if vitamin D deficiency has been corrected. Radiological evidence of healing rickets was assessed at one month and 3 months. X ray left wrist AP and knee joint AP view was taken for this purpose. Thacher score was done at follow up visits to see the degree of improvement. A radiologist's opinion was taken regarding x ray evidence of healing. After one month, all patients in the three groups were given vitamin D 400 units per day maintenance therapy and elemental Calcium 50 mg/kg/day in three divided doses for two months[15]. Children who do not show evidence of healing after 3 months of therapy were worked up for vitamin D resistant rickets.Children were observed for side effects of vitamin D toxicity. These include hypercalcemia (ca level >10.5 mg/dl), polyuria (>3 ml/kg/hr), pruritus, renal function impairment, nausea, constipation, arrhythmias or renal stones.

Treatment outcome was measured by Thacher Scoring System based on radiological findings. Maximum ten points were awarded. Complete healing was defined as

Thacher score ≤1.5 which was marked as cutoff for complete healing.All data collected was analyzed through (SPSS) version 20. Data which was quantitative in nature was shown as Mean ± SD.Data which was qualitative in nature was shown as frequency and percentage. The values of weight, height, hemoglobin, and biochemical parameters in the three treatment groups before and after treatment at 30 and 90 days were recorded and their statistical difference was measured by repeatesd measure ANOVA. Radiological findings and evidence of healing was observed in the three groups and assessed by means of Chi-square test. Chi-square will be applied to categorical data comparing patients who show evidence of complete healing versus those who don't heal completely with cutoff set at ≤1.5 for complete healing. A p- value of <0.05 was considered significant.

RESULTS

A total of 198 patients were enrolled in the 3 groups. The mean age in group-A was 14.76±9.10 months, in Group-B were 12.61±7.90 months and in group-C was 12.29±7.45 months with statistically same age distributions, p-value > 0.05. In group-A there were 46(70%) male and 20(30%) females, in Group-B there were 43(65%) male and 23(35%) were females while in Group-C there were 32(48%) male and 34(52%) female cases. Although in all study groups the weight was increased but in group-B the increase was more and significantly higher, p-value < 0.0001. Similarly height gain was also more common in group B (p<0.001). Table 1

There was more change (increase) in serum calcium level in group B as compared to other two groups (p<0.05). Similarly alkaline phosphatase level and serum vitamin D level as significantly high in group B than group A & C (p<0.05). Thacher score was although highly improved with group B, but the difference was insignificant among all groups (p>0.05). Efficacy was seen 65(98.5%) cases of Group-A and Group-B and 63(95.5%) cases of Group-C with no significant difference, p-value = 0.441. Table 3

Table 1: Baseline characteristics of children

	Group A	*Group B*	*Group C*
n	66	66	66
Age (Months)	14.76±9.10	12.61±7.90	12.29±7.45
Gender			
Male	46(70%)	43(65%)	32(48%)
Female	20(30%)	23(35%)	34(52%)
Weight (kg)			
Baseline	7.73±1.86	7.38 ±1.90	7.23±1.75
1st month	8.01±1.85	7.79±1.91	7.36±1.70
3rd month	8.36±1.79	8.48 ±1.91	7.59 ±1.67
Weight gain	0.635±0.28	1.09±0.55	0.36±0.31
Height (cm)			
Baseline	69.02±6.52	67.48±6.29	67.76±5.54
1st month	67.47±6.29	68.74±6.25	68.06±5.49
3rd month	67.76±5.44	71.53±6.32	68.56±5.54
Height gain	1.24±0.54	4.05±1.46	0.80±0.98

Table 2: Sign and symptoms of children n=198)

Table 3: Comparison of change in serum markersduring follow-up

Serum Calcium	*A*	*B*	*C*	*p-value*	*p-value*		
					A vs. B	*A vs. C*	*B vs. C*
Baseline	8.24±0.25	8.35±0.30	8.27±0.29	0.276	0.069	0.599	0.096
1st month	8.48±0.22	8.57±0.26	8.51±0.27	0.112	0.032	0.554	0.118
3rd month	8.82±0.29	9.04±0.33	8.83±0.34	0.009	<0.001	0.078	<0.001
Change	0.57±0.18	0.69±0.31	0.56±0.23	0.007	0.009	0.805	0.004
Alkaline phosphatase							
Baseline	1015.20±61.92	1120.55±188.54	1003.33±61.59	<0.001	<0.001	0.571	<0.001
1st month	928.74±39.99	954.52±55.05	929.73±38.71	0.001	0.001	0.901	0.002
3rd month	851.73±18.17	836.08±103.85	861.30±25.62	0.608	0.153	0.381	0.022
Change	163.47±55.35	284.47±178.86	142.03±57.76	<0.001	<0.001	0.278	<0.001
Vitamin D level							
Baseline	10.20±5.43	10.63±5.87	10.09±5.49	0.844	0.661	0.912	0.583
3rd month	17.91±6.75	21.06±6.65	18.57±7.14	0.022	0.009	0.580	0.038
Change	7.71±2.69	10.43±5.51	8.48±4.67	0.002	0.001	0.321	0.012
Thacher Score							
Baseline	8.63±1.67	8.11±2.29	8.33±1.75	0.051	0.584	0.060	0.073
3rd month	0.28±1.25	0.48±1.34	0.81±1.55	0.002	0.015	0.276	<0.001
Change	7.13±2.08	7.72±1.96	7.64±2.05	0.197	0.096	0.152	0.814
Efficacy (Thacher score ≤1.5)	65 (98.5%)	65 (98.5%)	63 (95.5%)	0.441			

DISCUSSION

Out of 198 cases, only 37 (18.68%) showed up with symptoms related to rickets like (bowing of legs 17, delay in walking 13, short stature 5). In the remaining children, rickets was diagnosed incidentally. In these patients, the majority presented with respiratory symptoms (pneumonia or bronchiolitis) (25.5%), sore throat (URTI) (18.18%), diarrhea (15.65%). The average age in our study was 14.76±9.10 months in group A, 12.61±7.90 months in group B and 12.29±7.45 months in group C. In a local study from Lahore, age of rickets children was in the range of 6-11 months[6].

On examination, most frequent clinical findings were wrist widening 98.98%, frontal bossing 90.90%, rachitic rosary 86.86%, protruded abdomen 57.57%, hypotonia 24.24%, genu varum 20.20%. Another study done earlier

showed that children with rickets mostly present with findings of wrist widening, irritable behavior, enlargement of head, bowing of legs etc. which supports our findings.[26]

In our study, we also gave importance to the increase in weight and height observed in the study groups. Treating rickets, results in remarkable improvement in weight and height. The best response was seen in injectable group- B when compared with oral group-A &C. At 3rd month the weight gain was higher in group-B (1.09±0.55kg) when compared to group-C (0.36±0.31kg) and was higher in group-A (0.635±0.28kg) when compared to group-C (0.36±0.31kg). The increase in weight was significantly higher in Group-B than A and C and in group-A than group-C, p-value < 0.0001. Similar results were obtained for increment in height with group B dominating. The height gain tends to be significantly higher in group-B (4.05±1.46cm) when compared to group-C (0.80±0.98cm) and group A(1.24±0.54cm), p-value < 0.05. Thus, treating rickets is an important therapeutic step in achieving adequate weight to prevent malnourishment and adequate height to prevent short stature.

Rickets is a disease caused by severe deficiency of vitamin D, and the highest frequency is seen in children between the ages of 3 and 18 months. Physical findings of rickets appear quite late, and disease can manifest before that with seizures due to hypocalcemia, irritable behavior, recurrent chest infections, failure to grow in height. Receiving adequate sunlight exposure is essential for synthesis of vitamin D. An infant needs 30 minutes of total body exposure or two hours ofexposure of head to sunlight in a week tosustain adequate level of vitamin D [27].In our study inadequate sun exposure was identified as the major risk factor for rickets present in 92.9% of patients. Breast feeding without adequate weaning diet, was present in 44.4% of the patients was another risk factor.Delayed weaning and improper weaning diet without adequate Vitamin D supplementation was identified in 26.6% of children. 8 children had family history of rickets and their siblings were diagnosed with rickets in follow-up visits.

Thacher score was done before and after treatment in study groups. All cases showed radiological evidence of healing at 4 and 12 weeks of treatment, irrespective of the treatment group. Almost all children in the three groups achieved radiological score of ≤1.5 indicative of complete healing at 12 weeks. A child in group B had no evidence of healing with Thacher score of 10 at 12 weeks and turned out to be vitamin D resistant rickets. Another child in group A failed to improve and was diagnosed as RTA. Three children in group C showed delayed healing as they forgot to take oral Calcium. But on resumption of calcium syrup their rickets, healed completely. Thus oral and injectable vitamin D are equally effective in reversing the radiological changes of rickets and producing complete healing.

A study reported higher male percentage of patients suffering from rickets i.e. there were 333 females (83%) and 67 males (17%).[28] In our study, we also found higher male to female ratio i.e. there were 121 (61%) male and 77(39%) female cases. This male gender dominance is the result of parents giving preference to male child over female, for getting medical care.A local study was done using oral vitamin-D (group-A) and injectable Vitamin-D (group-B). They included children between the ages of six months to three years. Children who had clinical, lab and x ray evidence of rickets, were enrolled in the study.The mean age was found to be 10.9±5.1 months in group-A& in group-B it was 14.7±8.1 months respectively.[24] In current study the mean age of the patients was 13.22 ± 8.21 months. The age distribution in this study is almost similar to above study.

In our study, biochemical parameters of calcium, phosphorus and alkaline phosphatase were compared in the three groups. The mean calcium levels at 1st and 2nd visit were also statistically same in all three study groups, p-value > 0.05. The mean calcium level at 3rd visit in group-B was 9.04±0.33 while the mean calcium level in group-A and Group-C, were 8.81±0.29 and 8.83±0.34 respectively, with significantly higher levels in group-B when compared to group-A and group-C, p-value < 0.001. In group-B the mean calcium levels were highly significantly improved, p-value < 0.05. The mean phosphate levels remained same in all three groups at each visit, p-value > 0.05, Serum phosphate levels were normal in 66(100%) of group-A, 65(98.5%) of group-B and 66(100%) of group-C, the normal phosphate levels were statistically same in all groups, p-value > 0.05.The mean phosphate levels equally improved from baseline till 3 month, with no group superior in improvement. The level of alkaline phosphatase was normalized in higher percentage of children in group B (77.3%) than group A(56.1%) and C(50.0%). So, we found out that injectable mega dose was superior to oral therapy in achieving normalization of biochemical parameters. In our study, no child developed documented hypercalcemia in any group, during 3 months of therapy.

In a local study, children in the age group of six months and three years were included. All these children had clinical, lab and X ray evidence of rickets. They reported higher mean weight and height at 90 days in injectable group when compared to oral group i.e. mean height at 90 days was 71.0±5.9 in oral groups and 73.4±7.1 in injectable group, p-value = 0.018, while mean weight at 90 days in oral and injectable group was 8.6±1.4kg and 9.0±2.0 kg, p-value = 0.027.[24]They further reported that at 90 days serum calcium level in oral and injectable was also comparable i.e. in oral and injectable was 8.8±0.7 and 8.7±0.9, p-value <0.05. The same was reported for alkaline phosphatase level.

Results of our study were different from above, as higher Calcium levels were obtained in the injectable group; also the decline in alkaline phosphatase was quicker in the injectable group. We also found at 3rd month the mean weight was higher in group-B (8.48±1.91 years) when compared to group-C (7.59±1.67 kg) and was higher in group-A (8.37±1.79±) when compared to group-C (7.59±1.67 kg), p-value < 0.05. The average height tends to be significantly higher in group-B (71.53±6.32 cm) when compared to group-C (68.56±5.54 cm), p-value < 0.05. So, alike our findings they concluded that both injectable and orally given vitamin D were successful in producing radiological healing but injectable form was more effective in achieving higher weight and height. There were no undesirable side effects and both forms of treatment were well-tolerated.[24]

In 2009, a prospective study was done. In this study, vitamin D was given as intramuscular injection in a dose of (10,000 IU/kg). Children were then followed for three months and their clinical, lab and x ray findings were compared. Most of the children (87.5%) in this study had sufficient vitamin D levels ≥20 ng/ml, but a small percentage(12.5%) had insufficient quantity of vitamin D. In approximately 95% of children, the x-ray changes of rickets were completely reversed. Hence, they concluded that a single intramuscular injection of vitamin D is a harmless and efficient way of treating severe rickets in children.[21] Our study, also showed like above study that stops dose of vitamin D in injectable form was able to correct lab findings and all x- ray findings of rickets in 3 months.

Another study was done in children with rickets between the ages of five months and five years. The children were divided into two groups, the first group received 60,000 vitamin D units in oral form every week for a period of ten weeks, and the second group was injected intramuscular vitamin D in a dose of 600,000IU. The study showed that lab values and x ray findings are equally corrected by the two groups. The study has concluded that divided oral and a single intramuscular injection of vitamin D are evenly efficacious in management of rickets.[29] Our results are different in respect of biochemical parameters. Radiological healing was equal in injectable and oral groups similar to above study. Vitamin D level was higher in injectable group compared to oral group in our study. Serum calcium level was higher in injectable group, also alkaline phosphatase decline was more in injectable group in our study showing different result from the above study.

In a recent study children were allocated into three treatment groups. In group A, children were given vitamin D3 in a dose of 4000IU/day along with elemental calcium in dose of 50mg/kg/day for a period of twelve weeks. In group B, children were given vitamin D3 in a dose of 30,000 IU per week along with elemental calcium in a dose of 50mg/kg/day for a period of twelve weeks. In group C, patients were given vitamin D3 as a single intramuscular injection of 300,000 IU along with elemental calcium in a dose of 50 mg/kg/day. After regimen completion, each child was put on maintenance dose of calcium and vitamin D. The result showed that vitamin D levels were highest in the injectable group C after three months when compared to the two oral groups. Thus, injectable vitamin D was more effective in achieving normal vitamin D levels as compared to oral groups. The three modes of treatment were similarly efficacious in enhancing the bone mineral concentration and density.[29] We also found higher efficacy of injectable medication.

Like above, in our study, the injectable group was able to achieve higher vitamin D levels as compared to oral group. The mean vitamin D level in injectable group B was 21.06±6.65 as compared to group A 17.91±6.75 and group C 18.57±7.14. After three months of therapy, only 70 (35.35%) children achieved sufficient Vitamin D levels (>20ng/ml). While the optimum Vitamin D level (>30ng/ml) was achieved only in 16 (8%) of the children. This is in sharp contrast to above study where all children were able to achieve normal vitamin D levels. Thus, it is shown that three months of treatment is not sufficient for correcting Vitamin D level and daily maintenance Vitamin D should be given for three more months at-least after completion of therapy. Our study demonstrates that even a mega dose of 200,000 units may not be enough to normalize level of vitamin D in Pakistani children with rickets. In children of Asian descent, vitamin D levels don't rise enough due to altered vitamin D metabolism caused by receptor mutation and complex changes in pharmacokinetic and pharmacodynamic properties of vitamin D.[30]

CONCLUSION

This study shows that injectable and oral (mega dose or daily) vitamin D were equally effective in producing complete radiological healing in children with rickets. It is concluded that Injectable vitamin D is superior to oral method of treatment as it produces higher vitamin D level and better corrects lab parameters in the form of higher Calcium level and lower alkaline phosphatase level, so it is advisable to give injectable vitamin D as compared to oral treatment.

Recommendation: We recommend daily vitamin D 400IU for less than one year old and 600IU for more than one year of age supplementation for at least 3 months after completion of therapy to achieve optimum vitamin D level.

REFERENCES

1. Greenbaum LA. Rickets and hypervitaminosis D. In: Behrman RE, Kliegman RM, Jenson HB, Stanton BF, editors. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: WB Saunders; 2016. p. 331-40.
2. Hatun S, Ozkan B, Orbak Z, Doneray H, Cizmecioglu F, Toprak D, et al. Vitamin D deficiency in early infancy. J Nutr 2005;135(2):279-82.
3. Wharton B, Bishop N. Rickets. The Lancet 2003;362(9393):1389-400.
4. Karim F, Chowdhury A, Gani M. Rapid assessment of the prevalence of lower limb clinical rickets in Bangladesh. Public Health 2003;117(2):135-44.
5. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357(3):266-81.
6. Ubaidullah MM, Rafique M, Sultan A. Analysis of risk factors for vitamin-D deficiency rickets in children below two years age. Pak Pediatr J 2008;32:82-6.
7. Wheeler BJ, Dickson NP, Houghton LA, Ward LM, Taylor BJ. Incidence and characteristics of vitamin D deficiency rickets in New Zealand children: a New Zealand Paediatric Surveillance Unit study. Austr N Z J PUb Health 2015;39(4):380-3.
8. Biser R, Ann, Hadley-Miller N. Vitamin D deficiency in breast-fed toddlers. Journal of Pediatric Orthopaedics 2001;21(4):508-11.
9. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008;122(2):398-417.
10. Chesney RW. Vitamin D and The Magic Mountain: the anti-infectious role of the vitamin. J of pediatrics 2010;156(5):698-703.
11. Rabea HM, Abdelrahim ME. The efficacy of oral versus parentral vitamin D in treatment of nutritional rickets. Med Sci 2012;1(4).
12. Holick MF. Vitamin D: a millenium perspective. JCell Biochem 2003;88(2):296-307.
13. Christakos S, Ajibaded V, d Hawan P, Fechner AJ, LJ M. Vitamin D: Metabolism.. Endocrinal Metab Clin North Am 2010;39:243.

14. Ozkan. B. Nutritional rickets.. J Clin Res Pediatr Endocrinol 2010;2(4):137-43.
15. Robinson PD, Högler W, Craig ME, Verge CF, Walker JL, Piper AC, et al. The re-emerging burden of rickets: a decade of experience from Sydney. Arch Dis Child 2006;91(7):564-8.
16. Najada AS, Habashneh MS, Khader M. The frequency of nutritional rickets among hospitalized infants and its relation to respiratory diseases. J Trop Pediatr 2004;50(6):364-8.
17. Chapman T, Sugar N, Done S, Marasigan J, Wambold N, Feldman K. Fractures in infants and toddlers with rickets. Pediatric radiology 2010;40(7):1184-9.
18. Balasubramanian S, Dhanalakshmi K, Amperayani S. Vitamin D deficiency in childhood—A review of current guidelines on diagnosis and management. Indian pediatrics 2013;50(7):669-75.
19. Emel T, Doğan DA, Erdem G, Faruk Ö. Therapy strategies in vitamin D deficiency with or without rickets: efficiency of low-dose stoss therapy. Journal of Pediatric Endocrinology and Metabolism 2012;25(1-2):107-10.
20. Sahay M, Sahay R. Rickets-vitamin D deficiency and dependency. Indian J Endocrinol Metab 2012;16(2):164-76.
21. Soliman AT, El-Dabbagh M, Adel A, Al Ali M, Aziz Bedair EM, Elalaily RK. Clinical responses to a mega-dose of vitamin D3 in infants and toddlers with vitamin D deficiency rickets. Journal of tropical pediatrics 2010;56(1):19-26.
22. Shah BR, Finberg L. Single-day therapy for nutritional vitamin D-deficiency rickets: a preferred method. The Journal of pediatrics 1994 Sep;125(3):487-90.
23. Cesur Y, Caksen H, Gündem A, Kirimi E, Odabaş D. Comparison of low and high dose of vitamin D treatment in nutritional vitamin D deficiency rickets. Journal of pediatric endocrinology & metabolism : JPEM 2003 Oct-Nov;16(8):1105-9.
24. Billoo AG, Murtaza G, Memon MA, Khaskheli SA, Iqbal K, Rao MH. Comparison of oral versus injectable vitamin-D for the treatment of nutritional vitamin-D deficiency rickets. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP 2009 Jul;19(7):428-31.
25. Shatsky M. Evidence for the use of intramuscular injections in outpatient practice. American family physician 2009 Feb 15;79(4):297-300.
26. Pettifor JM. Nutritional rickets. In: Glorieux FH, Pettifor JM, Juppner H, editors. Pediatric Bone. 2nd ed. London: Elsevier; 2012. p. 625-54.
27. Peng LF, Serwint JR. A comparison of breastfed children with nutritional rickets who present during and after the first year of life. Clin Pediatr 2003;42(8):711-7.
28. Mobini M, Kashi Z, Akha, Khani S, Bahar A. Comparing the Serum Levels of 25-hydroxyvitamin D after Taking Intravenous and Oral Vitamin D in Patients with Vitamin D Insufficiency. J Mazandaran Uni Med Sci 2016;25(133):48-57.
29. Mondal K, Seth A, Marwaha RK, Dhanwal D, Aneja S, Singh R, et al. A Randomized controlled trial on safety and efficacy of single intramuscular versus staggered oral dose of 600 000IU Vitamin D in treatment of nutritional rickets. Journal of tropical pediatrics 2014 Jun;60(3):203-10.
30. Rao YK, Midha T, Singh S, Bajpai A, Tilak A. Increment in vitamin D level and bone mineral accrual in children with vitamin D deficiency. Korean journal of pediatrics 2016 Jul;59(7):292-7