REVIEW ARTICLE

Biochemical parameters of rickets in Iranian children: A systematic review and meta-analysis

Kourosh Sayehmiri[1], Masoumeh Shohani[2], Gholamreza Kalvandi[3], Reza Najafi[4], Hamed Tavan[5]

[1]Professor of Biostatistics, School of Medicine, Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, Iran, [2]Assistant Professor, PhD of Nursing, Department of Nursing, Faculty of Nursing and Midwifery, Ilam University of Medical Sciences, Ilam, Iran, [3]Associate Professor of Pediatrics Gastroenterology, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran, [4]Assistant Professor of Pediatric Endocrinology & Metabolism, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran, [5]Faculty of Nursing and Midwifery, Student Research Committee, Ilam University of Medical Sciences, Ilam, Iran

Background: Many causes can lead to childhood rickets. We aimed to investigate the biochemical symptoms of childhood rickets with systematic review and meta-analysis. **Materials and Methods:** Seven articles published from 1975 to 2018 were recruited. The literature search was performed in the Scientific Information Database, Google Scholar, PubMed, and Elsevier databases using related keywords. For meta-analysis, the results of the studies were pooled using the random-effects model. The heterogeneity between the studies was checked using Q test and I^2 index. **Results:** The total sample population consisted of 933 children with biochemical symptoms of rickets (133 participants per article). According to our findings, the mean serum levels of PO_4, Ca, and alkaline phosphatase in children with rickets were 4.18 (95% confidence interval [CI]: 3.75–4.61, $I^2 = 98.3\%$, $P < 0.001$), 9.23 (95% CI: 8.78–9.68, $I^2 = 99.6\%$, $P < 0.001$), and 1.33 (95% CI: 1.23–1.44, $I^2 = 95.6\%$, $P < 0.001$), respectively. **Conclusion:** Characterizing the biochemical symptoms of rickets in children can help to early diagnose and prevent the disease in children. Furthermore, educating parents about biochemical symptoms can lead to early diagnosis and successful treatment of rickets in children.

Key words: Biochemical symptoms, childhood, meta-analysis, rickets, systematic review

How to cite this article: Sayehmiri K, Shohani M, Kalvandi G, Najafi R, Tavan H. Biochemical parameters of rickets in Iranian children: A systematic review and meta-analysis. J Res Med Sci 2019;24:76.

INTRODUCTION

Rickets or bone softness is a disease associated with delayed bone growth in infants and children.[1,2] In this disease, children's bones remain soft, which increases the risk of bone loss and bone fractures. The main cause of rickets is Vitamin D deficiency; however, calcium deficiency has also been noted as an etiologic factor.[3,4] Children with malnutrition are at higher risk of rickets.

In general, rickets is known as a childhood disease; nevertheless, it also occurs in adults. Following groups are at higher risk of rickets: (a) infants whose mothers were not adequately exposed to the sunlight; (b) people with lactose intolerance who do not use complete milk; and (c) infants whose mothers suffered from Vitamin D deficiency during pregnancy.[5,6] Vitamin D is essential for the intestinal absorption of calcium. In the absence of this Vitamin, calcium is not absorbed, and the bones and teeth become defective. If the condition progresses to a deteriorating process, the muscles also become weak.[7,8]

Butter, egg, fish liver oil, margarine, milk, and fatty fish such as tuna, as well as fish and salmon, are among Vitamin D rich foods.[9,10] Rickets may rarely be a hereditary illness linked to a dominant allele on chromosome X disrupting the phosphate reabsorption and Vitamin D metabolism.[8]

Signs of rickets include bone softness and bone pain, dental growth defects, premature rot, muscle weakness, increased risk of bone fracture, curvature and defects in bone formation, growth retardation, calcium

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_354_18

Address for correspondence: Hamed Tavan, Faculty of Nursing and Midwifery, Student Research Committee, Ilam University of Medical Sciences, PO Box: 69391-77143, Ilam, Iran. E-mail: hamedtavan@gmail.com

Received: 05-08-2018; **Revised:** 19-12-2018; **Accepted:** 05-05-2019

deficiency, muscle weakness, and abnormal skull softness in newborns.[11,12] The curvature is a "classic" symptom of rickets that occurs in the bones of the legs and chest. This defect may also occur in the skull deteriorating its elliptical state. In severe conditions, the curvature also appears in the long bones and the vertebral column. These tendrils are generally treated in childhood.[13,14]

Rickets is diagnosed by blood tests, X-rays of the bones, blood gas analysis, and bone biopsy.[15,16] Rickets can be prevented and treated with administrating a diet rich in Vitamin D (generally in the form of Vitamin D3 tablets), phosphates, and liver oil, as well as by exposure to sunlight.[17,18]

The causes and symptoms of rickets have been addressed by several studies worldwide. Performing meta-analyses are necessary to validate the results of these studies. The aim of this systematic review and meta-analysis was to determine the characteristics, causes, biochemical symptoms, and mineral deficiencies (Ca, alkaline phosphatase [ALP], and PO4) in Iranian children with rickets.

MATERIALS AND METHODS

Search strategy

This was a systematic review and meta-analysis evaluating the literature published on childhood rickets. Electronic databases, including Google Scholar, Scientific Information Database, PubMed, Scopus, Web of science, and Elsevier, were searched. The articles published in Persian and English were recruited. The keywords included rickets, rickets in Iran, biochemical symptoms of rickets, complications of rickets, and consequence of rickets in Iran. The literature published from 1975 to 2018 were included in the study.

Selection of studies and data extraction

Two investigators independently performed the initial search. Those studies addressing the primary outcomes of interest on rickets (i.e., causes and consequences of rickets in Iran) were selected. The studies that solely assessed the treatment of rickets were excluded from the study. A standardized data extraction template was used to prepare a primary checklist of the included studies. This checklist included the author's name, article title, year of publication, location of the study, sample size, population, gender, weight, and height. Furthermore, the biochemical symptoms of rickets, including the serum levels of PO_4, Ca, and ALP, were recorded in individual genders and age categories. The final checklist was generated by selecting the studies that met the qualification criteria. Accordingly, 80 studies entered into the primary checklist. Among these, 50 articles were include after reading the titles. The 30 selected articles were reassessed for the secondary outcomes of interest, as well as for sample size, the time of data collection and biochemical symptoms of rickets. Finally, seven articles met the qualification criteria to be included in the meta-analysis. The full texts of these articles were finally assessed [Figure 1].

Statistical analysis

The normal distribution model was used to analyze the data. The weight of each study was inversely proportional to its variance. The heterogeneity among the studies was checked using the Q test and I^2 index. Due to the significant heterogeneity among the studies, we used a random effects model for meta-analysis. Meta-regression was used to explore the reasons of heterogeneity. The statistical analyses were performed in STATA software, version. 11 (College Station, TX, USA).

RESULTS

The biochemical symptoms of Iranian children with rickets had been reported in the seven included studies published from 1975 to 2018. The total combined sample size was 933 (133 participants per article). The characteristics of the included studies and their geographical distribution are presented in Table 1.

Figure 2 shows the biochemical parameters (serum levels of PO_4, Ca, and ALP) in Iranian children with rickets. The means of serum levels of PO_4, Ca, and ALP were obtained as 4.18 [95% confidence interval (CI): 3.75–4.61, $I^2 = 98.3\%$, $P < 0.001$, Figure 2a], 9.23 [95% CI: 8.78–9.68, $I^2 = 99.6\%$,

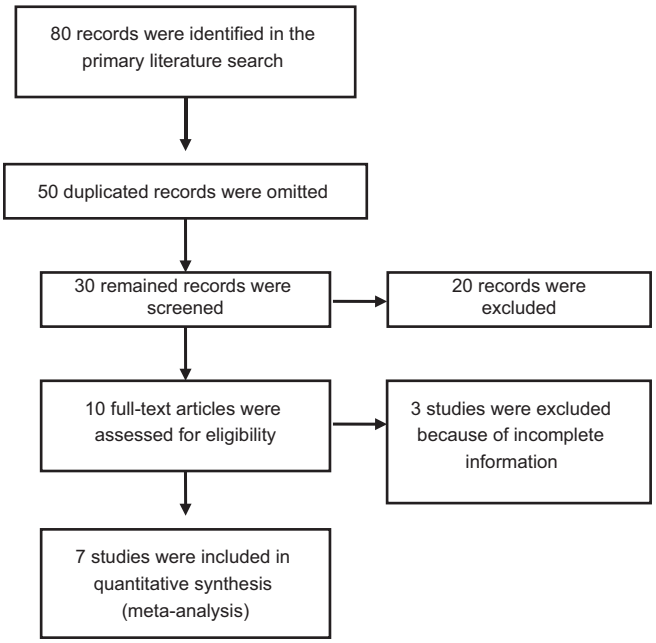

Figure 1: Flowchart of the present systematic review and meta-analysis

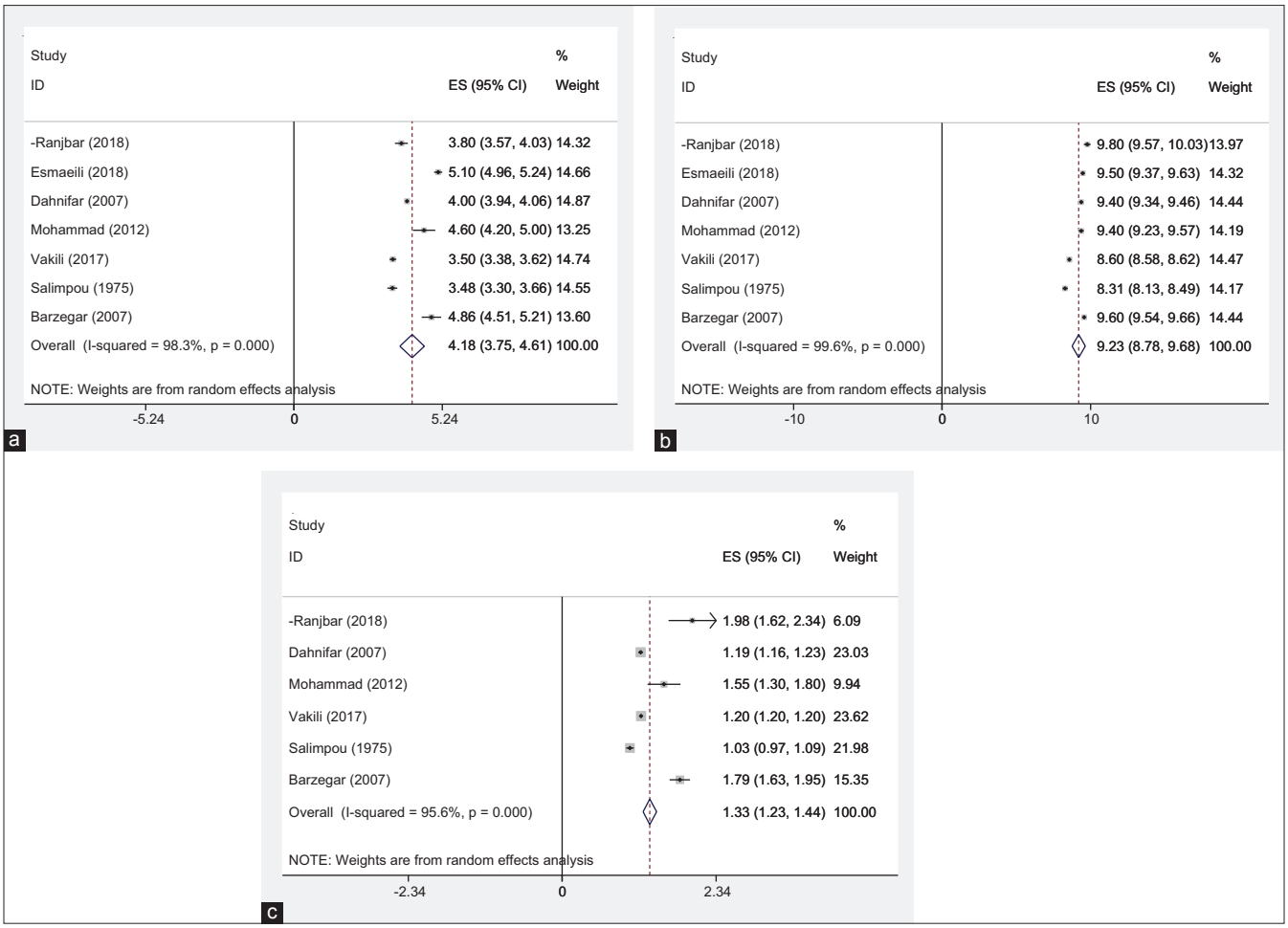

Figure 2: (a) The mean serum PO4 level with 95% confidence interval in the studies included in the meta-analysis. Each line shows the 95% confidence interval. The diamond shows the overall effects of the studies. The mean serum PO4 level in children with either partial or complete rickets using the random effects model. Each square represents the effect estimated for individual studies. The confidence interval of the mean PO4 serum level is reflected by the size of each square, which is proportional to the weight assigned to each study. The diamond represents the overall pooled results. (b) The mean serum Ca level with 95% confidence interval in the studies included in the meta-analysis. Each line shows the 95% confidence interval. The diamond shows the overall effects of the studies. (c) The mean serum alkaline phosphatase level with 95% confidence interval in the studies included in the meta-analysis. Each line shows the 95% confidence interval. The diamond indicates the overall effects of the studies. The overall mean serum alkaline phosphatase level in children with either partial or complete rickets using the random effects model. Each square represents the effect estimated for individual studies

Table 1: The biochemical parameters in Iranian children with rickets

References	First author	Year	Sample size	Girl	Boy	PO_4	Ca	ALK
[19]	Ranjbar	2018	12	-	-	3.8	9.8	1.98
[20]	Esmaeili	2018	119	68	51	5.1	9.5	-
[21]	Dahnifar	2007	414	414	0	4.0	9.4	1.194
[22]	Mohammadi	2012	48	21	27	4.6	9.4	1.55
[23]	Vakili	2017	100	-	-	3.5	8.6	1.2
[24]	Salimpour	1975	200	73	127	3.48	8.31	1.03
[25]	Barzegar	2007	40	10	30	4.86	0.96	1.79

ALK=Alkaline phosphatase

$P < 0.001$, Figure 2b], and 1.33 [95% CI: 1.23–1.44, $I^2 = 95.6\%$, $P < 0.001$, Figure 2c], respectively.

Meta-regression analysis indicated that the studies with lower sample sizes reported higher levels of the biochemical parameters in Iranian children with rickets [Figure 3a]. The trend of biochemical parameters over time in children with rickets is shown in Figure 3b. This indicated an increasing trend in the biochemical symptoms of rickets from 1975 to 2018. Figure 4 depicts a symmetric funnel plot implying no publication bias in the included studies. Level of heterogeneity in this study was 95.6%, which indicates there were high heterogeneous among studies.[26]

DISCUSSION

The aim was to determine the causes and symptoms of rickets in Iranian children. The minerals (i.e., Ca, ALP, and PO4) deficiencies were assessed as biochemical indicators of rickets using meta-analysis.

The altered metabolisms of Vitamin D, calcium, and phosphorus in children can manifest as rickets and bone deformation. In fact, nutritional deficiencies and

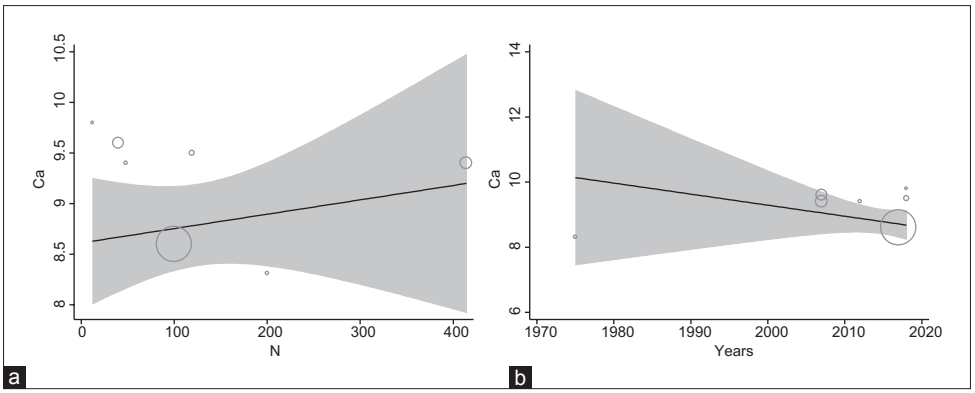

Figure 3: (a) Meta-regression analysis according to the sample size. (b) Meta-regression analysis according to the year of publication. An increasing trend in biochemical parameters was observed in Iranian children with rickets from 1975 to 2018

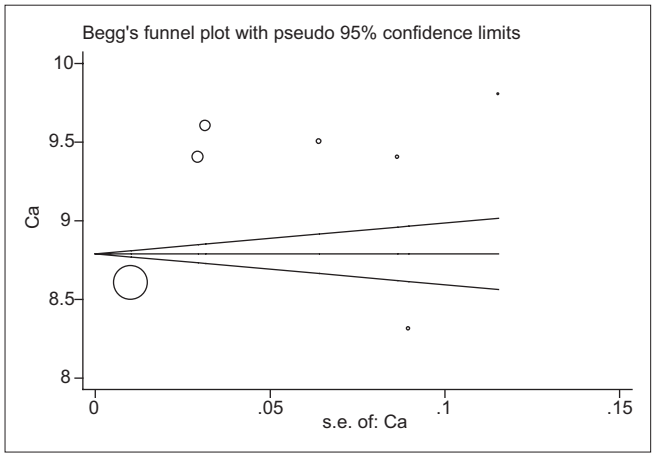

Figure 4: Publication bias in the studies reporting the biochemical parameters in Iranian children with rickets. The symmetric funnel plot implied no publication bias among the included studies

poor dietary intakes of Vitamin D and calcium are the main etiologies for rickets.[1] Determining the levels of Vitamin D3, parathyroid hormone, ALP, creatinine, calcium, phosphorus, and blood urea nitrogen can be beneficial to establish the diagnosis of rickets.[11,12]

In the present meta-analysis, the mean serum PO_4 level was found to be lower than normal in Iranian children with rickets. Other studies have also reported similar findings.[25,27] Poor nutritional status during pregnancy and childhood can predispose children to phosphate deficiency. Therefore, this condition may be preventable by educating parents to consume foods such as meat and milk which contain protein phosphates. A diet rich in calcium and protein can also provide the phosphorus needed by the body. Bread made from whole grains and legumes also contain high levels of phosphorus.[24,23]

We also found that the mean serum Ca level was lower than normal in Iranian children with rickets, which is consistent with other studies.[12,27] Poor nutritional intake is also the main cause of Ca deficiency. Consuming milk and other dairy products such as ice cream can be helpful in preserving an adequate level of Ca within the body. Infants who are solely breast-fed are particularly at risk of Ca deficiency as breast milk alone cannot provide all the Ca needs. Therefore, administrating simultaneous Ca supplementation is recommended to avoid calcium deficiency in infants and children.[27-29] Educating pregnant or lactating mothers about the nutritional needs of infants and providing them with appropriate breast-feeding schedules may be beneficial to meet the nutritional needs of infants.

Similarly, we noticed that the mean serum level of ALP was lower than normal in Iranian children with rickets. Considering the role of ALP in bone reabsorption, ALP deficiency can exaggerate bone deformation in children with rickets. ALP deficiency in children with rickets may be secondary to either malnutrition or the presence of underlying diseases.[11,13,28,29]

In present systematic review and meta-analysis, we identified that the frequency of rickets was higher in boys than girls among the included studies. This was in parallel to the results of previous studies.[22-25] Other studies have also indicated a higher incidence of rickets in boys than girls[27,30,31], which is in line with our observation. This may be in part related to early diagnosis of rickets in boys due to their higher physical activities and the nature of their movements. Nevertheless, there is still no explanation for this phenomenon, and this should be addressed in future studies.

Most children with rickets are diagnosed in the first 2 years of their lives. As rickets is more likely to present at this period, it is advisable to closely monitor children <2 years old to predict and prevent the formation of rickets.

Studies have shown an increasing incidence in childhood rickets in some regions of the world. Feeding children

with milk enriched with Vitamin D is a viable strategy to prevent the disease in countries with a high prevalence of rickets.[32] Although all Iranian infants receive about 400 units Vitamin D per day after the first 2 weeks of life, rickets still occurs in Iranian children.[27] This indicates that parents are not adequately educated regarding the nutritional requirements of children. By providing such educations, it may be possible to eradicate rickets among Iranian children.

Limitations

There were several limitations in the studies included in the present meta-analysis. There were no clear distinctions between Vitamin D levels and the types of movements in some studies. We were also unable to assess all biochemical parameters of rickets in some geographical areas of Iran due to the lack of respective studies in these areas.

CONCLUSION

The prevalence of rickets was higher in boys than girls. By timely and precise detection of biochemical characteristics of rickets, it is possible to prevent this disease in children. Social educations about the biochemical symptoms of rickets are crucial to early diagnose and successfully treat rickets in children.

Acknowledgments

Thanks to the Deputy of Research and Technology of Ilam University of Medical Sciences for supporting the project financially. This was a research project approved by the Ethics Committee of Research of Ilam University of Medical Sciences (Ethical code: IR.MEDILAM.REC.1397.140).

Financial support and sponsorship

Ilam University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Pitt MJ. Rickets and osteomalacia are still around. Radiol Clin North Am 1991;29:97-118.
2. Thacher TD, Fischer PR, Tebben PJ, Singh RJ, Cha SS, Maxson JA, *et al.* Increasing incidence of nutritional rickets: A population-based study in Olmsted county, Minnesota. Mayo Clin Proc 2013;88:176-83.
3. Kazeminezhad B, Taghinejad H, Borji M, Tarjoman A. The effect of self-care on glycated hemoglobin and fasting blood sugar levels on adolescents with diabetes. J Compr Ped 2018;9:e62661. doi: 10.5812/compreped.62661.
4. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, *et al.* The 2011 report on dietary reference intakes for calcium and Vitamin D from the institute of medicine: What clinicians need to know. J Clin Endocrinol Metab 2011;96:53-8.
5. Taylor JA, Richter M, Done S, Feldman KW. The utility of alkaline phosphatase measurement as a screening test for rickets in breast-fed infants and toddlers: A study from the puget sound pediatric research network. Clin Pediatr (Phila) 2010;49:1103-10.
6. Khalil T. Prevalence of rickets among children below one-year encounter of North West armed forced hospital in Tabuk. Int J Med Sci Public Health 2014;3:827-31.
7. Colak A, Yildiz O, Toprak B, Turkon H, Halicioglu O, Coker I, *et al.* Correlation between calcium and phosphorus in cord blood and birth size in term infants. Minerva Pediatr 2016;68:182-8.
8. Singleton R, Lescher R, Gessner BD, Benson M, Bulkow L, Rosenfeld J, *et al.* Rickets and Vitamin D deficiency in Alaska native children. J Pediatr Endocrinol Metab 2015;28:815-23.
9. Uush T. Prevalence of classic signs and symptoms of rickets and Vitamin D deficiency in Mongolian children and women. J Steroid Biochem Mol Biol 2013;136:207-10.
10. Abdul-Razzak KK, Ajlony MJ, Khoursheed AM, Obeidat BA. Vitamin D deficiency among healthy infants and toddlers: A prospective study from Irbid, Jordan. Pediatr Int 2011;53:839-45.
11. Gartner LM, Greer FR. Section on Breastfeeding and Committee on Nutrition. American Academy of Pediatrics. Prevention of rickets and Vitamin D deficiency: New guidelines for Vitamin D intake. Pediatrics 2003;111:908-10.
12. Pettifor JM. Rickets and Vitamin D deficiency in children and adolescents. Endocrinol Metab Clin North Am 2005;34:537-53, vii.
13. Tarjoman A, Vasigh A, Safari S, Borji M. Pain management in neonatal intensive care units: A cross sectional study of neonatal nurses in Ilam city. J Neonatal Nurs 2018;8:6. [doi: 10.1016/j.jnn.2018.08.006].
14. Braithwaite V, Jarjou LM, Goldberg GR, Prentice A. Iron status and fibroblast growth factor-23 in Gambian children. Bone 2012;50:1351-6.
15. Thacher TD, Fischer PR, Isichei CO, Zoakah AI, Pettifor JM. Prevention of nutritional rickets in Nigerian children with dietary calcium supplementation. Bone 2012;50:1074-80.
16. Braithwaite V, Prentice AM, Doherty C, Prentice A. FGF23 is correlated with iron status but not with inflammation and decreases after iron supplementation: A supplementation study. Int J Pediatr Endocrinol 2012;2012:27.
17. Kemi VE, Kärkkäinen MU, Rita HJ, Laaksonen MM, Outila TA, Lamberg-Allardt CJ, *et al.* Low calcium: Phosphorus ratio in habitual diets affects serum parathyroid hormone concentration and calcium metabolism in healthy women with adequate calcium intake. Br J Nutr 2010;103:561-8.
18. Oduwole AO, Giwa OS, Arogundade RA. Relationship between rickets and incomplete distal renal tubular acidosis in children. Ital J Pediatr 2010;36:54.
19. Hasani-Ranjbar S, Ejtahed HS, Amoli MM, Bitarafan F, Qorbani M, Soltani A, *et al.* SLC34A3 intronic deletion in an Iranian kindred with hereditary hypophosphatemic rickets with hypercalciuria J Clin Res Pediatr Endocrinol 2018;10:343-9.
20. Esmaeili Dooki M, Moslemi L, Moghadamnia AA, Alijanpour Aghamaleki M, Bijani A, Pornasrollah M, *et al.* Children with Vitamin D deficiency: Is A wrist X-ray necessary? Arch Iran Med 2018;21:589-94.
21. Dahifar H, Faraji A, Yassobi S, Ghorbani A. Asymptomatic rickets in adolescent girls. Indian J Pediatr 2007;74:571-5.
22. Mohammadi B, Najafi M, Farahmand F, Motamed F, Ghajarzadeh M, Mohammadi J, *et al.* Prevalence of Vitamin D deficiency and rickets in children with cholestasis in Iran. Acta Med Iran 2012;50:482-5.
23. Ghazi AA, Zadeh-Vakili A, Zarif Yeganeh M, Alamdari S, Amouzegar A, Khorsandi AA, *et al.* Hereditary Vitamin D resistant rickets: Clinical, laboratory, and genetic characteristics of 2 Iranian siblings. Int J Endocrinol Metab 2017;15:e12384.

24. Salimpour R. Rickets in Tehran. Study of 200 cases. Arch Dis Child 1975;50:63-6.
25. Barzegar M, Baradaran R, Gafarpour Sakha K, Mahbobi L, Shiva S, Ashrafi Hafez A. Infantile nutritional rickets and Vitamin D status of mothers. J Tabriz Univ Sci 2007;29:33-7.
26. Sayehmiri K, Tavan H, Sayehmire F, Mohamadi I. Prevalence of epilepsy in Iran using meta-analysis and systematic review. ZUMSJ 2015;23:112-1. Available from: http://zums.ac.ir/journal/article-1-3094-en.html. [Last accessed on 2018 Apr 04].
27. Shiva S, Barzgar M. Contributing factors in hypocalcemic seizure due to nutritional rickets. Tabriz Univ Med Sci Health Serv 2008;30:75-8.
28. Badfar G, Shohani M, Nasirkandy MP, Mansouri A, Abangah G, Rahmati S, *et al.* Epidemiology of hepatitis B in pregnant Iranian women: A systematic review and meta-analysis. Arch Virol 2018;163:319-30.
29. Badfar G, Shohani M, Mansouri A, Soleymani A, Azami M. Vitamin D status in Iranian pregnant women and newborns: A systematic review and meta-analysis study. Expert Rev Endocrinol Metab 2017;12:379-89.
30. 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;91:564-8.
31. Weisberg P, Scanlon KS, Li R, Cogswell ME. Nutritional rickets among children in the United States: Review of cases reported between 1986 and 2003. Am J Clin Nutr 2004;80:1697S-705S.
32. Rodd C, Mushcab SA. Hypocalcemic seizures secondary to nutritional Vitamin D deficiency in 3 infants fed soy formula. Clin Pediatr (Phila) 2005;44:455-7.