HK J Paediatr (new series) 2016;**21**:70-73

Original Articles

Is Increased Serum Alkaline Phosphatase Level in Children a Sign of Vitamin D Deficiency or Bone Growth?

LJ ***Yu***, H ***Wang***, H ***Liang***, LL ***Guo***

Abstract ***Objective:*** This study aims to investigate the effects of vitamin D and alkaline phosphatase (AKP) on height. ***Method:*** 1887 healthy children were enrolled from May 2014 to December 2014 for the detection of height, AKP, 25(OH)-vitamin D3 [25(OH)D], and serum levels of Calcium (Ca) and Phosphorus (P) at 3 different time points (baseline, 3-month and 6-month). In accordance with the growth speed, the children were divided into the low-speed group (<1 cm/3 months), the middle-speed group (1~2 cm/3 months) and the high-speed group (>2 cm/3 months) to compare the differences of the above indicators among the groups. ***Results:*** The enrolled children all had normal serum Ca, and the calcium-phosphorus product was >40, while 98.5% children exhibited the increased serum phosphorus. The high-speed group exhibited significantly increased AKP concentration, which was statistically significant with the other two groups (P<0.05); and the 25-(OH)-VitD3 levels of all groups were low and had no significant difference. ***Conclusions:*** The children enrolled had normal serum Ca, but the low 25(OH)D level suggested vitamin D deficiency. The high concentration of AKP signified rapid growth.

Key words Alkaline phosphatase; Height; Vitamin D

Introduction

Vitamin D was essential for calcium absorption and for maintaining bone health in the paediatric population.[1] More than 50% of the world's population was at risk for vitamin D deficiency.[2] The absorption and utilisation of vitamin D were closely related to sunlight. Therefore, ensuring adequate exposure to sunlight had great value for preventing rickets.[3] If the mother lacked vitamin D inside her body during pregnancy, it could result in fetal congenital rickets,[4] and if the child suffered from nutritional vitamin D deficiency in the overall growth and development period, it would cause Calcium (Ca) and Phosphorus (P) metabolism disorders affecting his/her growth and development, namely vitamin D deficiency rickets,[5] characterised by abnormal calcification of epiphyseal cartilage plate,[6] including caput quadratum, hand-foot bracelet, rib edge eversion, beaded rib, X-shaped legs, O-shaped legs, chicken breast, pectus excavatum and dental caries,[7] etc. Furthermore, there would also be impacts towards many other aspects. For example, the skin might exhibit eczema; the muscle might exhibit ligamentous laxity; and the infant might express laryngeal osteomalacia, and would be susceptible for cough, laryngitis, bronchiolitis[8] and asthmatic suffocating pneumonia, as well as digestive diseases.[9] Because it could seriously harm the growth, development and health of children, it was one of "the four diseases in children" that China paid high attention and strength for the prevention and treatment.[10] The primary prevention, as well as the timely diagnosis and treatment of rickets, were the important measures to reduce the harms of rickets.[11] Vitamin D deficiency prevailed in epidemic proportions all over the Indian subcontinent, with a prevalence of 70%-100% in the general population.[12]

Child Care Department of The Second Affiliated Hospital of Harbin Medical University, 148 Baojian Road, Nan Gang District, Harbin, Heilongjiang Province, China

LJ **Yu** (于立君) *PhD*
H **Wang** (王慧) *Master of Medicine*
H **Liang** (梁虹) *Master of Medicine*
LL **Guo** (郭麗麗) *Master of Medicine*

Correspondence to: Dr LJ **Yu**

Received June 16, 2015

Presently, the diagnosis of rickets mainly depended on the facts that the serum calcium was decreased, while the serum phosphorus was normal, the calcium (in mg/dL) and phosphorus (in mg/dL) product was <40, and AKP was increased; but the clinical practices in recent years found that although some children exhibited the calcium and phosphorus product >40, their AKPs were still higher than the normal, so the significance was thought-provoking. This study measured the serum contents of AKP and 25(OH)D in children aged 0-14 years, aiming to analyse the relationships between elevated AKP level and vitamin D deficiency.

Materials and Methods

Subjects

1887 healthy children that visited the Department of Child Health, the Second Affiliated Hospital of Harbin Medical University, from May 2014 to December 2014, were selected, including 1107 males and 780 females, aged 40 days~14 years. All patients had no fever, cold, diarrhoea, pneumonia, other infectious diseases and such chronic organic diseases as tuberculosis, etc. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Harbin Medical University. Written informed consent was obtained from all participants' guardians.

Height Measurement

The heights of all the children were measured at baseline, and at 3-month and 6-month, respectively. The height measurement was performed by a trained nurse in accordance with the uniform standards. The height measuring meter was used to measure the height before 10:00, with error <0.2 cm. The children were then divided into the low-speed group (<1 cm/3 months), the middle-speed group (1~2 cm/3 months) and the high-speed group (>2 cm/3 months) according to their growth speed in the past six months.

Laboratory Tests

For all the children, the fasting serum calcium, serum phosphorus, AKP and 25(OH)D (Roche reagent, Basel, Switzerland) were measured at baseline, and the calcium and phosphorus product was calculated. The concentrations of total 25(OH)D, including 25(OH)D3 and 25(OH)D2, were detected using high performance liquid chromatography (HPLC) (Agilent 1100 HPLC available from Agilent Technologies of Palo Alto, Calif).

Statistical Analysis

SPSS19.0 software was used for the statistical analysis. The results among the groups were analysed by the t test and the Bonferroni correction, with the significant difference set as P=0.05/3 = 0.0167.

Results

Serum Ca and P

All the 1887 children exhibited serum Ca within the normal range, 98.5% children exhibited the increased serum P, and 1.5% children exhibited normal serum P; the calcium phosphorus products of all the children were greater than 40.

AKP and 25(OH)D

The comparison of different growth-speed groups revealed that the average AKP value was the highest in the high-speed group, followed by the middle-speed group and the low-speed group. The pairwise comparison showed the statistical significance between every 2 groups (P<0.0167, Table 1). At the same time, those of the middle-speed group and the high-speed group were higher than the normal reference value (36~213 U/L); while the vitamin D levels of different groups showed no significant difference (P>0.0167), and those of the middle- and low-speed group were lower than the normal level (26~65 ng/L).

Discussion

Vitamin D deficiency rickets or vitamin D deficiency had been the most common childhood nutritional deficiency

Table 1 Relationships of AKP and 25 (OH)D with the growth speed in children

Group	AKP (U/L)	25(OH)D (ng/L)
Low-speed	161.25±12.52	24.82±15.65
Middle-speed	225.32±52.43*	25.62±18.68
High-speed	292.26±22.62*$^{\nabla}$	26.88±13.45

Note: Compared with the low-speed group, *P<0.0167; compared with middle-speed group, $^{\nabla}$P<0.0167

disease in Chinese children, especially in the northern area.[13] Because China had vast areas, the distances to the sun and the sunshine-exposing hours varied significantly from place to place, and when combined with the impacts of haze and other factors, the northern region showed the characteristics of significantly higher incidence and more severe disease situations. The conventional vitamin D supplement could not effectively prevent the situations of vitamin D deficiency in northern children.[14]

The results of this study showed that regardless of the growth speed, the serum calcium levels of the children enrolled were normal, while most children were associated with the increased serum phosphorus, and AKP was increased or normal while vitamin D was reduced, so the increased AKP was not the direct evidence of vitamin D deficiency.

It was considered in the past that the bone alkaline phosphatase (BAKP) was a subtype of alkaline phosphatase isoenzymes, which was synthesised by bone cells. When the body was in calcium malnutrition, the serum calcium concentration would be decreased, and the concentration of parathyroid hormone would be increased, thus promoting the kidney to synthesise 25(OH)D3, and the latter could activate the still osteoblasts, so the osteocytes would exhibit feedback active proliferation. Thus large amounts of BAKP would be synthesised and released into the blood. The increase signified the biological onset of rickets, albeit in the subclinical state. The increased levels were closely related to the activity of rickets.[15-17] Another fact worth mentioning was that even if the adults with closed epiphysis exhibited serious vitamin D deficiency, only the content of 25(OH)D would be decreased, and AKP would not be increased,[18] unless accompanied by new bone formation.[19] Therefore, AKP was just an index of growth rather than an index of vitamin D deficiency.

As for normal healthy children, the AKP increase would normally mean that the recent growth was more rapid, and so the amount of vitamin D needed would be relatively large. Because BAKP existed only inside the hypertrophic chondrocytes of the epiphyseal growth plate, it could promote bone formation. Specifically, AKP in the blood is mainly derived from hypertrophic chondrocytes of the epiphyseal growth plate, and less of AKP comes from liver and kidney. In growing children, AKP is mainly derived from BAKP that is generated by the epiphyseal growth plate due to fewer concentrations in liver and kidney. Therefore, BAKP was significantly positively correlated with the serum AKP, and could be replaced by AKP.[20,21]

Through comparing the children with different growth speeds, it was found that the faster the growth speed, the higher the average AKP level, therefore, it could be speculated that AKP was the indicator of child's recent growth speed, while not directly associated with the vitamin D levels.

All the children had normal serum calcium levels while low vitamin D levels, suggesting that in the growing period of children, the supplement of vitamin D should be further strengthened to make up the deficiency, to meet the growing demands, and also to include the demands from normal metabolism.

Conflict of Interest

All authors have no conflict of interest regarding this paper.

References

1. Lee JY, So TY, Thackray J. A review on vitamin d deficiency treatment in paediatric patients. J Pediatr Pharmacol Ther 2013; 18:277-91.
2. Holick MF. Sunlight, ultraviolet radiation, vitamin D and skin cancer: how much sunlight do we need? Adv Exp Med Biol 2014; 810:1-16.
3. Karczmarewicz E, Czekuć-Kryśkiewicz E, Płudowski P. Effect of vitamin D status on pharmacological treatment efficiency: Impact on cost-effective management in medicine. Dermatoendocrinol 2013;5:1-6.
4. Paterson CR, Ayoub D. Congenital rickets due to vitamin D deficiency in the mothers. Clin Nutr 2015;34:793-8.
5. Kelishadi R, Farajzadegan Z, Bahreynian M. Association between vitamin D status and lipid profile in children and adolescents: a systematic review and meta-analysis. Int J Food Sci Nutr 2014; 65:404-10.
6. Glorieux FH, Pettifor JM. Vitamin D/dietary calcium deficiency rickets and pseudo-vitamin D deficiency rickets. Bonekey Rep 2014;3:524.
7. Wranicz J, Szostak-Wêgierek D. Health outcomes of vitamin D. Part I. characteristics and classic role. Rocz Panstw Zakl Hig 2014; 65:179-84.
8. Gröber U, Spitz J, Reichrath J, Kisters K, Holick MF. Vitamin D: Update 2013: From rickets prophylaxis to general preventive healthcare. Dermatoendocrinol 2013;5:331-47.
9. Robinson PD, Högler W, Craig ME, et al. The re-emerging burden of rickets: a decade of experience from Sydney. Arch Dis Child 2006;91:564-8.
10. Fraster DR. Vitamin D-deficiency in Asia. J Steroid Biochem Mol Biol 2004;89-90:491-5.
11. Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. Dermatoendocrinol 2013;5:51-108.
12. Ritu G, Gupta A. Vitamin D deficiency in India: prevalence, causalities and interventions. Nutrients 2014;6:729-75.

13. Xiao JP, Zang J, Pei JJ, Xu F, Zhu Y, Liao XP. Low maternal vitamin D status during the second trimester of pregnancy: a cross-sectional study in Wuxi, China. PLoS One 2015;10: e0117748.
14. Li PL, Tian YJ, Wang YH, et al. The prevalence of vitamin D deficiency among schoolchildren: a cohort study from Xinxiang, China. J Pediatr Endocrinol Metab 2015;28:629-33.
15. Rennie LM, Beattie TF, Wilkinson AG, Crofton P, Bath LE. Incidental radiological diagnosis of rickets. Emerg Med J 2005; 22:534-7.
16. Ambroszkiewicz J, Rowicka G, Chelchowska M, Gajewska J, Strucińska M, Laskowska-Klita T. Biochemical markers of bone metabolism in children with cow's milk allergy. Arch Med Sci 2014;10:1135-41.
17. Çetin G, Eşkazan AE, Ar MC, et al. Bone-Specific Alkaline Phosphatase Levels among Patients with Multiple Myeloma Receiving Various Therapy Options. Turk J Haematol 2014;31: 374-80.
18. Sanford M, McCormack PL. Eldecalcitol: a review of its use in the treatment of osteoporosis. Drugs 2011;71:1755-70.
19. Sirtori P, Sosio C, Resmini G, Rubinacci A. Effect of short course of 1,25-dihydroxyvitamin D3 on biochemical markers of bone remodelling in postmenopausal women. Pharmacol Res 1996;33: 353-9.
20. Arends S, Spoorenberg A, Efde M, et al. Higher bone turnover is related to spinal radiographic damage and low bone mineral density in ankylosing spondylitis patients with active disease: a cross-sectional analysis. PLoS One 2014;9:e99685.
21. Heanu RP. Functional indices of vitamin D status and ramification of vitamin D deficiency. Am J Clin Nutr 2004;80:1706-9S.