Original Article/Özgün Makale

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.766043
J Health Sci Med 2020; 3(4): 389-394

Predicting vitamin D deficiency through parathormone in the children of a small city located in the warm climate belt of Northern Hemisphere

Kuzey Yarımküre'de ılıman iklim kuşağındaki küçük bir ilde parathormon üzerinden D vitamini eksikliğini öngörme

Gökce Celep[1], Zeynep Hülya Durmaz[2]

[1]Amasya University Medical Faculty, Sabuncuoğlu Şerefeddin Education and Research Hospital, Department of Paediatrics, Amasya, Turkey
[2]Amasya University Medical Faculty, Sabuncuoğlu Şerefeddin Education and Research Hospital, Department of Biochemistry, Amasya, Turkey

Cite this article as/Bu makaleye atıf için: Celep G, Durmaz ZH. Predicting vitamin D deficiency through parathormone in the children of a small city located in the warm climate belt of Northern Hemisphere. J Health Sci Med 2020; 3(4): 389-394.

ABSTRACT

Aim: The aim of this study is to analyse the serum levels of parathormone (PTH), calcium (Ca), phosphorus (P), vitamin D and define a cut off value for vitamin D deficiency and insufficiency in a sample of healthy children.

Method: A total of 543 healthy children enrolled to this study. The data of parathormone, Ca, P, 25 (OH) D levels, season of blood sample collection, age, sex and health status were collected from the hospital record system retrospectively. The relationships between these variables were defined by statistical analyses and explained in detail in the text.

Results: The inflection point that triggered parathormone rise was 13.6 ng/ml. The optimal level (50p) was 20.3 ng/ml for preadolescent group, 18.3 ng/ml for male adolescents and 18.1 ng/ml for female adolescents. Logistic regression analyses pointed that age, parathormone and seasons contributed to vitamin D status.

Conclusion: The habitat is a significant variable for vitamin D status because altitude and latitude affect solar Zenith angle. Age, gender and seasonal variations must be taken in consideration when recommending supplementation.

Keywords: Vitamin D deficiency, 25 (OH) D, PTH, latitude, child

ÖZ

Amaç: Bu çalışmanın amacı bir grup sağlıklı çocukta parathormon (PTH), kalsiyum (Ca), fosfor (P), D vitamini düzeylerini ortaya koymak ve "D vitamini eksikliği" ile "yetersizliği" tanıları için düzey saptamaktır.

Yöntem: Çalışmaya bilinen kronik sağlık sorunu olmayan 543 çocuk katıldı. Parathormon, Ca, P, 25 (OH) D düzeyleri, kan örneğinin alındığı mevsim, yaş, cinsiyet ve sağlık durumuna ait veriler hastane kayıt sisteminden geriye dönük olarak elde edildi. Değişkenler arasındaki ilişkiler metinde ayrıntılı olarak tanımlanan istatistiksel yöntemlerle değerlendirildi.

Bulgular: Parathormon yükselmesini tetikleyen en düşük parathormon değeri 13,6 ng/ml olarak saptandı. Farklı yaş grupları için 25 (OH) D düzeyi persentil değerleri hesaplandı, buna göre ideal 25 (OH) D düzeyi (50 persentil) ergenlik öncesi grupta 20,3 ng/ml, ergen erkeklerde 18,3 ng/ml, ergen kızlarda 18.1 ng/ml olarak saptandı. Yaş, parathormon ve mevsimin D vitamini düzeylerine katkısı olduğu lojistik regresyon analizleri ile gösterildi.

Sonuç: Yaşanılan yerin rakımı ve enlemi güneşin Zenith açısını etkilediğinden D vitamini durumunda önemli bir değişkendir. Destek ve tedavi yaklaşımında yaş, cinsiyet ve mevsimler dikkate alınmalıdır.

Anahtar Kelimeler: D vitamini eksikliği, 25 (OH) D, PTH, enlem, çocuk

Corresponding Author/Sorumlu Yazar: Gökce Celep, Amasya Üniversitesi Tıp Fakültesi, Sabuncuoğlu Şerefeddin Eğitim ve Araştırma Hastanesi, Pediatri Anabilim Dalı, Amasya, Türkiye
E-mail/E-posta: gokce4celep@yahoo.com
Received/Geliş: 07.07.2020 **Accepted/Kabul:** 13.08.2020

INTRODUCTION

Vitamin D is a steroid hormone and a fat-soluble vitamin (1). It is synthesized in the skin under direct sunlight. The provitamin form, 7-dehydrocholesterol, is converted to Vitamin D3 upon ultraviolet B rays with the wave band of 290-315 nm (1). The efficiency of cutaneous vitamin D synthesis depends on the intensity of sunlight, surface area of the skin exposed to the direct sunlight, duration of exposure, the zenith angle of the sun, thickness and color of the skin (2,3). Seasons, time of the day, indirect sunlight exposure, sunscreens, clothes preventing sunlight exposure, aging, lived latitude, outdoor activities, physical exercise and obesity affect this transformation rate (1). It is hydroxylated in the liver and kidneys to create the active form: 1, 25 dihydroxy vitamin D. The dietary intake of vitamin D is limited unless fortified food is not consumed. The content of vitamin D in breast milk is poor and oily fish, yolk sac; the richest food sources, contain little amounts (1,4). Also, vitamin D insufficiency (VDI) and VDD may be the result of genetic factors influencing the metabolism of the vitamin (5).

Vitamin D is the key nutrient for healthy skeletal system. Calcium (Ca) and phosphorus (P) absorption is under the control of parathormone (PTH)–vitamin D interaction. The precision balance between these markers provide the homeostasis of bone turnover and healthy growing up (1,6). When serum Ca decreases PTH secretion increases to mobilize Ca from bones. Vitamin D regulates PTH secretion on this basis and increases intestinal Ca absorption (7). The inverse proportion between PTH and vitamin D (the metabolite for laboratory evaluation is 25 (OH) D) is already known, but the inflection point of PTH may vary between populations or geographic areas. Ca and PTH are reliable parameters for laboratory evaluations, but P and ALP may be affected from environmental conditions, especially hemolysis which is common in pediatric blood samples (1,8). The lowest level of 25 (OH) D that triggers PTH secretion is defined as "vitamin D deficiency (VDD)" and this process disrupts bone mineralization whereas sufficient vitamin D levels provide PTH plateau to provide homeostasis (9). In addition, vitamin D has other crucial roles in other tissues where its receptors exist, including cardiovascular, neurologic, gastrointestinal, immune and endocrine systems. Deficiency may result in multisystem health troubles because regulation of approximately 1000 genes and nuclear transcription factors disrupts (5). Immune modulation troubles in case of deficiency leading to autoimmune diseases, recurrent infections, cancers or the rate of exacerbations of chronic illnesses increases (10,11). In critically or chronically ill children, if there is vitamin D deficiency, replacement and supplementation can provide better outcomes (12). Thus, VDD is an important public health problem especially for growing up children (6). However, sufficiency can be evaluated via its relationship with PTH, but this may reflect its only role in Ca-P metabolism. It is unclear whether serum PTH suppression is an appropriate method for determining optimal vitamin D levels in children and adolescents for other metabolic effects.

The optimal vitamin D level providing all metabolic effects has not been clearly defined. Diagnosis of VDD is methodologically challenging because of various measurement techniques (radioimmunoassay, competitive protein binding assays (CPBA), high pressure liquid chromatography (HPLC), and liquid chromatography-tandem mass spectrometry). These methods may yield different results about 10-25% range (13). Available assays can measure 25 (OH) D levels, the product of the reactions in the liver. It is the main indicator of vitamin D status since it has a longer half-life than the active form. Also, there is lack of consensus about "adequate" serum 25 (OH) D levels, considering the skeletal and non- skeletal effects (6). Various cut off points for VDD have been adopted by various organizations and authors (14-16). Differences in the study groups, geographic areas (different altitudes and latitudes) or techniques to determine 25 (OH) D levels lead to conflicts in VDD definition (17).

VDD prevalence is a common public health problem in the pediatric population (18,19). It is observed that children and their mothers spend more time indoors and less for outdoor activities. Consumption of sunscreens has increased recently and clothing habits may prevent direct sunlight exposure (20,21). The aim of this study is to evaluate the serum levels of 25 (OH) D, PTH, Ca, P, alkaline phosphatase (ALP) and to define VDD and VDI in a sample of healthy children in a small city of Turkey, a country located in the warm climate belt of northern hemisphere.

MATERIAL AND METHOD

This retrospective and cross-sectional study was conducted in pediatric outpatient clinics of a secondary health care center in middle northern Turkey within two years. The source of data was the medical records of the participants, investigated through the hospital information system (Sisoft, HBYS ®). Children younger than 1 year old were excluded from the study because they were supposed to be under the cover of national Vitamin D supplementation campaign of

Health Ministry of Turkish Republic. In addition, patients having chronic diseases or weight and height measurements other than 3 to 97 percentiles according to the growth charts based on age and sex for Turkish children, the ones having metabolic defects in Ca and vitamin D metabolism and taking vitamin D or multivitamin preparations were excluded from the study. A total of 543 healthy children aged 1 to 17 years old were enrolled. Weights were measured with a calibrated digital scale and heights with a stadiometer before physical examination. Venous blood samples for laboratory studies were obtained from all participants in the morning, 8.00-12.00 am. Serum levels of 25 (OH)D were measured by electrochemiluminescence immunoassay method (Siemens Advia Centaur XP®, Erlangen Germany). The specificity and sensitivity of the method was 98% and 95% respectively with coefficient of variation value 6.8. PTH levels were analysed by electrochemiluminescence method (Siemens Advia Centaur XP®, Erlangen Germany) and the blood samples for PTH testing were transported to laboratory in cold conditions. ALP, Ca were tested by kinetic color test method and P levels were measured by molybdate UV test method (Beckman Coulter AU 5800®, Brea California, United States). All tests were performed immediately after taking the blood samples. For the evaluation of the results the participants were divided into four age groups: 1-4 years (preschool), 5-8 years (middle childhood), 9-12 years (early adolescence), and 13-17 years (adolescence).

Statistical analyses

Statistical analyses were performed by using SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL, USA). The data were presented as frequencies and percentages for categorical variables and as median, interquartile range (IQR), minimum–maximum, range or mean±SD, percentiles for scale variables by descriptive statistics, when indicated. The distribution patterns of variables were investigated by visual (histograms, probability plots) and analytical (Kolmogorov Simirnov test) methods. As the serum 25 (OH) D, age, PTH, ALP levels were non -normally distributed in the whole group, Kruskall Wallis tests were conducted to compare their levels among seasonal and gender groups. Mann Whitney U test was performed to test the significance of pairwise differences using Bonferroni corrections to adjust for multiple comparisons. Ca and P, normally distributed variables, were analyzed by t-test. In addition, all variables (Ca, P, ALP, PTH, 25 (OH) D) were distributed normally within preadolescent and adolescent age groups so they were analyzed by t-test. The Chi-square test or Fisher's exact tests were also used to compare categorical variables in different groups. The correlation associations were calculated by using Spearman test. The 25 (OH) D level that triggers PTH secretion was analyzed by using Receiver Operating Characteristics (ROC) analyses. The areas under ROC curves were calculated. For some ROC analyses the participants were divided into age groups as "prepubertal" (≤10 years old) and "pubertal" (>10 years old). The variables that contribute 25 (OH) D status were tested via logistic regression analyses to form an equation model. The clearness of the model was tested by Nagelkerke R2 and Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. A 5% type 1 error level was used to infer statistical significance ($p<0.05$).

Ethics

This study was approved by the local committee of non-invasive scientific researches with decision no: 27/02/2020-E.5675.

RESULTS

This study was conducted with 543 children aged 1 to 17 (median: 5; IQR: 8) years old in a small city located in the warm climate belt of the north hemisphere (36°57'06"-36°31'53"eastern meridians and 41°04'54"-40°16'16"northern parallels). The participants consisted of 296 (54.5%) females and 247 (45.5%) males. Approximately 60% of the blood samples were collected in summer and autumn. The median concentrations of 25 (OH) D, PTH, ALP were 18.7 ng/dl (IQR: 15.9), 39 pg/ml (IQR: 24.2), 200 IU/L (IQR: 81.5), mean concentrations of Ca and P were 9,7±0.4 mg/dl; 4.9±0.7 mg/dl respectively. Serum PTH levels were high (>65 pg/ml) in 10.3% (n=56) of the study group.

The median of 25 (OH) D levels in males was 21.4(IQR:16.9) ng/ml and 17.0 (IQR: 14.1) ng/ml in females, the difference was significant statistically ($p<0.0001$). In addition, PTH and P values were also different, but there was no significant difference in Ca, ALP concentrations between sexes. 25 (OH) D, PTH, Ca, P, ALP levels were all statistically different between age groups ($p<0.001$). The median 25 (OH) D concentrations were different in each seasonal group, with higher levels in summer and autumn ($p<0.0001$). Age and 25 (OH) D levels were inversely correlated ($p<0.001$; r=-266) (**Table**). Additionally, 25 (OH) D and PTH levels were inversely correlated ($p<0.001$; r=-272). The correlation was not significant between 25 (OH) D and Ca ($p=0.08$; r=0.077).

Table. 25 (OH) D, PTH, Ca, P, ALP levels according to age, sex, season (Page 7)

	AGE (years) median (IQR)	25 (OH) D (ng/ml) median (IQR)	PTH (pg/ml) median (IQR)	CALCIUM (mg/dl) mean ±SD	PHOSPHORUS (mg/dl) mean ±SD	ALP (IU/ml) median (IQR)
SEX						
Males (n=247)	4.0 (8)	21.40 (16.90)	34.70 (27.35)	9.7±0.4	5.0±0.7	202.0 (78.0)
Females (n=296)	5.0 (8)	17.0 (14.13)	41.10 (22.60)	9.6±0.4	4.8±0.7	197.0 (90.0)
p		<0.001	0.003	0.164	0.026	0.266
SEASON						
Spring	6.0(8)	13.55 (11.0)	40.90 (23.90)	9.7±0.4	4.8±0.7	199.5 (89.7)
Winter	5.0 (9)	11.58 (11.64)	38.10 (27.40)	9.6±0.3	4.7±0.6	191.0 (92.0)
Autumn	4.0 (7)	20.0 (13.90)	36.30 (25.0)	9.7±0.4	5.0±0.7	201.0 (82.0)
Summer	5.0 (8)	25.10 (12.20)	38.70 (23.50)	9.6±0.4	5.0±0.6	203.5 (82.0)
p		<0.001	0.115	0.625	0.002	0.435
AGE						
Pre-adolescent (≤10 years old)	4.1±2.8	21.8±1.0	39.6±2.2	9.7±0.4	5±0.6	217±86.3
Adolescent (>10 years old)	13.7±1.9	15.8±1.0	51.0±2.3	9.5±0.3	4.2±0.7	174.1±98.2
p		<0.0001	<0.0001	0.0002	<0.0001	<0.0001

The ROC analyses for this study group revealed that the inflection point of 25 (OH) D to trigger PTH rise was 13.6 ng/dl and this cut off value had 58.9% sensitivity with 70% specificity for identification of vitamin D deficiency (p<0.0001; area under the curve (AUC): 0.656; 95% confidence interval (CI): 0.61-0.76). Thirty-three percent (n= 179) of the participants had 25(OH) D levels <13.6 ng/dl, referring VDD. The median age of VDD group was 7 (IQR: 9) and the median age of the participants having sufficient 25 (OH) D levels (>13.6ng/ml) was 4 (IQR: 6). Age was a statistically significant variable for 25 (OH) D status. PTH concentrations were significantly higher in deficiency and lower in sufficiency groups with median values 43.8 pg/ml (IQR: 28.2) and 37.3 pg/ml (IQR: 23.5) respectively (p<0.001). Approximately 60% of the participants having high PTH levels (>65pg/ml) had VDD. Mean Ca levels of the deficiency and sufficiency groups were 9,7±0,4 and 9,6±0,4 mg/dl, but the difference was not significant (p= 0.11). Six (1.1%) of the participants had hypocalcemia (serum Ca level<8.8 mg/dl) and 5 of them had VDD. Median ALP and mean P levels revealed statistical significance between two groups (p=0.006; p<0.0001). Hypophosphatemia (serum P level<3.8mg/dl) was detected in 37 (6.8%) of the participants and 67.6% (n=25) of them had VDD which was also a significant finding (p<0.001). ROC analyses were performed for females and males considering age groups as preadolescence (≤10 years old) and adolescence (>10 years old), but cut off values of 25 (OH) D deficiency could not be determined statistically. The results were analyzed to calculate the values of 50p for age groups. The optimal level (50p) was 20.3 ng/ml for preadolescent group, 18.3 ng/ml for male adolescents and 18.1 ng/ml for female adolescents.

Logistic regression analyses pointed that age, PTH and seasons contributed to poor vitamin D status. Each one-year increase in age, increased VDD risk 1.08-fold (p=0.012). Also, one-unit increase in PTH levels increased the risk of low 25 (OH) D status 1.015-fold (p=0.021). The prominent risk factor was seasonal changes as VDD risk increased 16.3 folds in winter (Nagelkerke R2=0.369; Hosmer Lemeshow test p=0,520)

DISCUSSION

In this study 543 healthy children aged between 1to 17 were evaluated for vitamin D status through 25 (OH) D, circulating metabolite of active vitamin D, and its metabolic interactions with Ca, P, ALP and PTH. The study was conducted in a small city of northern Turkey where the estimated maximum monthly average global solar radiation ranged from 20.05 to 23.71 MJ/m^2 (22,23). In this country, children younger than 1 year old are under the cover of national Vitamin D supplementation campaign of Health Ministry of Turkish Republic. Three drops of cholecalciferol solution that contains 133 IU vitamin D3 in each drop is recommended and provided freely to all infants younger than one year old by this campaign (24). 25 (OH) D levels decreased with age and it had higher levels in summer and autumn as a gift of direct sunlight exposure. Females had lower 25 (OH) D levels than males and this became more apparent with increasing age. The inflection point for VDD of this study population was detected to be 13.6 ng/ml. The optimal value (50p) of 25 (OH) D for preadolescent age group (≤10 years old) was 20.3 ng/ml. It was calculated to be 18.3ng/ml for adolescent males and 18.1 ng/ml for adolescent females.

Vitamin D has a crucial role in Ca- P metabolism and healthy growing up of the skeletal system during childhood and adolescence (6). Moreover, multisystem effects of VDD or VDI cause problems in the homeostasis of the whole body. Many studies have proved that VDD or VDI is a global public health problem contributing to disturb skeletal, mental, immunological, metabolic, cardiovascular harmony (25). Physiologically 25 (OH) D and PTH has inverse correlation whereas Ca and P are positively correlated with 25 (OH) D. In this study group 57 participants had hyperparathyroidism and 57.9% (n=33) of them had low 25 (OH) D levels (<13.6 ng/ml). The rate of hyperparathyroidism may be lower than expected because PTH rise becomes apparent within four weeks in case of VDD (26). Additionally, hypocalcaemia and hypophosphatemia rates were higher in VDD group, to be expected. The levels of P are higher and ALP levels are lower than expected in this study which is thought to be a result of hemolysis caused during blood sample punctuation procedure. All variables were statistically different between preadolescents and adolescents ($p<0.0001$).

The efficiency of vitamin D -25 (OH) D can be evaluated via its relationship with PTH and most of the studies have been based on this concept. In 2015, Endocrine Society defined vitamin D status with a consensus statement and the cut off value was determined to be <30 nmol/ml (<12ng/ml; 1 ng/ml=2.5 nmol/l.) to prevent nutritional rickets (14). The American Academy of Pediatrics (AAP) defined deficiency for values <15 ng/ml; insufficiency for values between 15 and 20 ng/ml; sufficiency for values between 20 and 100 ng/ml (15). A study from Korea including 193 children aged between 2 months and 17 years old defined the inflection point of 25 (OH) D due to PTH as 18ng/ml. The health status of the study group was mixed. The data were based on hospital records as in our study (27). Crews et al. (28) defined the lowest 25 (OH) D level as 10ng/ml in child population having no renal insufficiency. Also, Atapattu et al. (9) evaluated 214 children having no conditions related with Ca-P metabolism and concluded that the biochemical abnormalities are demonstrated when 25 (OH) D level was <34 nmol/l (13.6 ng/ml), similar to the results of this study. However, Hill et al. (17) analyzed the levels of PTH and 25 (OH) D in 735 healthy children aged between 7-18 in three different sites having different latitudes in USA and could not define an inflection point. They concluded that their inability to clearly identify an inflection point of serum 25 (OH) D for maximal suppression of serum PTH for healthy children and adolescents was because of fast growing up and bone turnover. Age and sex should be taken in consideration because of differences in growing up patterns (29). In this study, the inflection point of 25 (OH) D was detected as 13.6ng/ml for the whole study group. Our results were compatible with literature supporting Atapattu et al. (9) and Hill et al. (17). We defined the optimal levels (50p) for preadolescent and adolescent age groups as vitamin D has crucial roles not only in skeletal system, but homeostasis as well.

Here, vitamin D status of a healthy child population was presented, but this study has several limitations: It was a retrospective study based on hospital records. The study group had a small size and did not reflect the whole population. Also, the number of participants was not sufficient to determine the inflection point of VDD according to age and gender. Dietary habits, skin colour, sunlight exposure history, clothing habits of the participants were not mentioned. The pubertal stage of the adolescent group, which is important for bone turnover, was not in consideration. There was no data about rickets and radiologic findings to support vitamin D effects at different levels of 25 (OH) D. In addition, the accuracy of 25(OH) D measurement techniques may vary and technical standardization is usually difficult.

CONCLUSION

We recommend that the inflection point of serum 25 (OH) D level that triggers PTH rise is 13.6 ng/ml for our latitude. The habitat may cause variations in optimal 25 (OH) D levels as altitude and latitude affect solar zenith angle which is directly related with sunlight exposure. In addition, seasons and sex must be taken in consideration when recommending supplementation as winter and spring provides poor sunlight which limits skin synthesis and females are more prone to deficiency. Since PTH levels increase apparently four weeks after deficiency onset, we recommend that target levels of 25 (OH) D levels (for the same latitude) should be taken in consideration while deciding supplementation (20.3 ng/ml for preadolescents, 18.3 ng/ml for adolescent males and 18.1 ng/ml for adolescent females). However, high doses of vitamin D can be prescribed when 25 (OH) D is <13.6 ng/dl and PTH levels are increased and/or biochemical and radiologic signs of rickets occur.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the local committee of non-invasive scientific researches with decision no: 27/02/2020-E.5675.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr 1995; 6: 638–45.
2. Wahl DA, Cooper C, Ebeling PR, et al. A global representation of vitamin D status in healthy populations. Arch Osteoporos 2012; 7: 155–72.
3. Grant WB, Strange RC, Garland CF. Sunshine is good medicine: the health benefits of ultraviolet-B induced vitamin D production. J Cosmet Dermatol 2003; 2: 86–98.
4. Reeve LE, Chesney RW, DeLuca HF. Vitamin D of human milk identification of biologically active form. Am J Clin Nutr 1982; 36: 122-6.
5. Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet 2010; 376: 180–8.
6. Antonucci R, Locci C, Clemente MG, Chicconi E, Antonucci L. Vitamin D deficiency in childhood: old lessons and current challenges. J Pediatr Endocrinol Metab 2018; 31: 247–60.
7. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA 2005; 294: 2336–41.
8. Bikle D. Vitamin D: an ancient hormone. Exp Dermatol 2011; 20: 7-13.
9. Atapattu N, Shaw N, Hogler W. Relationship between serum 25- hydroxyvitamin D and parathyroid hormone in the search for a biochemical definition of vitamin D deficiency in children. Pediatr Res 2013; 74: 552-6.
10. Holick MF. Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. South Med J 2005; 98: 1024–7.
11. Holick MF. The vitamin D deficiency pandemic and consequences for non-skeletal health: mechanisms of action. Mol Aspects Med 2008; 29: 361–8.
12. Sankar J, Ismail J, Das R, Dev N, Chitkara A, Sankar J. Effect of severe vitamin D deficiency at admission on shock reversal in children with septic shock: A prospective observational study. J Intensive Care Med 2017; 20: 1-7
13. Enko D, Fridrich L, Rezanka E, et al. 25-hydroxy-vitamin D status: limitations in comparison and clinical interpretation of serum-levels across different assay methods. Clin Lab 2014; 60: 1541–50.
14. Munns CF, Shaw N, Kiely M, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab 2016; 101: 394–415.
15. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M, Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008; 122: 398–417.
16. Braeger C, Campoy C, Colomb V, et al. ESPGHAN Committee on Nutrition. Vitamin D in the healthy European paediatric population. JPGN 2013; 56: 692–701.
17. Hill KM, McCabe GP, McCabe LD, Gordon CM, Abrams SA, Weaver CM. An inflection point of serum 25-hydroxyvitamin D for maximal suppression of parathyroid hormone is not evident from multi-site pooled data in children and adolescents. J Nutr 2010; 140: 1983-8.
18. Akman AO, Tümer L, Hasanoğlu A, İlhan M, Çaycı B. Frequency of vitamin D insufficiency in healthy children between 1 and 16 years of age in Turkey. Pediatr Int 2011; 53: 968–73.
19. Şahin ÖN, Serdar M, Serteser M, Ünsal İ, Özpınar A. Vitamin D levels and parathyroid hormone variations of children living in a subtropical climate: a data mining study. Ital J Pediatr 2018; 44: 40.
20. Erkuran N, Gücük S. Relationship between vitamin D levels and demographic factors and life style characteristics of 18-49 age women. Euras J Fam Med 2017; 6: 35-42.
21. Seo JH, Chung HJ, Kim HJ, et al. Increasing vitamin D deficiency in children from 1995 to 2011.Turk J Pediatr 2016; 58: 616-22.
22. Location. (Amasya Valiliği web site). Available at http://www.amasya.gov.tr/cografi-konum. Accessed in September 2018.
23. Tarhan S, Sarı A. Model selection for global and diffuse radiation over the Central Black Sea (CBS) region of Turkey. Energy Conversion and Management 2005; 46: 605-13.
24. Hatun S, Ozkan B, Bereket A. Vitamin D deficiency and prevention: Turkish experience. Acta Pediatr 2011; 100: 1195-9.
25. Wimalawansa SJ. Non-musculoskeletal benefits of vitamin D. J Steroid Biochem Mol Biol 2018; 175:60-81.
26. Kroll MH, Bi C, Garber CC, et al. Temporal relationship between vitamin D status and parathyroid hormone in the United States. PLoS ONE 2015; 10: e0118108.
27. Kang JI, Lee YS, Han YJ, Kong KA, Kim HS. The serum level of 25-hydroxyvitamin D for maximal suppression of parathyroid hormone in children: the relationship between 25- hydroxyvitamin D and parathyroid hormone. Korean J Pediatr 2017; 60: 45-9.
28. Crews BO, Moore J, Dietzen DJ. Circulating intact parathyroid hormone is suppressed at 25-hydroxyvitamin D concentrations >25 nmol/L in children. J Pediatr Endocrinol Metab 2014; 27: 657-60.
29. Harkness L, Cromer B. Low levels of 25-hydroxy vitamin D are associated with elevated parathyroid hormone in healthy adolescent females. Osteoporos Int 2005; 16: 109-13.