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Original Article

Defining a cutoff point for vitamin D deficiency based on insulin resistance in children

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ABSTRACT

Background: Vitamin D deficiency is a common worldwide problem. Low levels of serum 25-hydroxy vitamin D [25(OH)D], as a marker of vitamin D deficiency, have been linked to a wide field of health problems, including metabolic diseases such as insulin resistance, type 1 and type 2 DM. There is no universal definition for cutoff value of vitamin D deficiency and it seems that it varies in different populations.

Objective: Most previous studies have used a start rise of PTH as a criteria to detect threshold of serum 25(OH)D, However, the aim of this study was to determine a cutoff point of serum 25(OH)D for vitamin D deficiency based on HOMA-IR.

Materials and methods: Two hundred and ninety seven healthy children (aged 7–11 years) were enrolled. Serum 25(OH)D and PTH were measured and HOMA-IR was calculated. The ROC curve was utilized to obtain a cutoff of vitamin D deficiency based on HOMA-IR.

Results: 25(OH)D concentrations were inversely correlated with HOMA-IR levels (Spearman's $r = -0.14$, $p = 0.016$). Serum 25(OH)D cutoff point was 11.6 ng/mL (29 nmol/L) in relation with HOMA-IR >2.1. By using this cutoff value, the prevalence of vitamin D deficiency was 43.4% in this study population of healthy children.

Conclusion: We found that serum 25(OH)D levels are inversely associated with insulin resistance. These results suggest that in MetS patients it may benefit to determine cutoff value of 25(OH)D levels based on HOMA-IR.

1. Introduction

Vitamin D deficiency is common worldwide problem [1–4] and a prevalent disorder in developing countries like Iran [5–9]. Documented risk factors for deficiency of vitamin D are obesity, racial/ethnicity, female sex, winter season, malnutrition, lack of sun exposure and covered clothing style.

Zanjan province in Northwest of Iran has a sunny climate with 4 seasons including cold winter and mild summer, which should favor plentiful cutaneous production of vitamin D. However, this region, like other Middle East countries, negatively impacted by urbanization resulting in life style shifts toward sedentary activity, lack of sunlight exposure, and unhealthy dietary patterns, which lead to high prevalence of vitamin D deficiency in adults [9–12] and children [6,13].

Recent epidemiological, observational and interventional studies of elderly adults [14–17], young adults [18], and children [19–22] have suggested that low levels of serum 25-hydroxy vitamin D (25(OH)D), the recognized indicator of total vitamin D status in the body, are linked with some components of metabolic syndrome (MetS) like insulin resistance, obesity, dyslipidemia and hypertension. MetS predisposes to increased risk for diabetes, cardiovascular events and some other chronic diseases.

There is no consensus on the optimal levels of serum 25(OH)D worldwide; however vitamin D deficiency is usually defined by 25(OH)D serum concentration <20 ng/mL (50 nmol/L), vitamin D

Abbreviations: BMI, body mass index; BP, blood pressure; ECLIA, electrochemiluminescence; FBS, fast blood sugar; FPG, fasting plasma glucose; GPs, general practitioners; HPMA-IR, homeostatic model assessment; iPTH, intact parathyroid hormone; IR, insulin resistance; MetS, metabolic syndrome; 25(OH)D, 25-hydroxy vitamin D; PTH, parathyroid hormone; ROC curve, receiver operating characteristic curve; WC, waist circumference.

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insufficiency (mild deficiency) as a serum 25(OH)D of 21–29 ng/mL (51–74.5 nmol/L) and vitamin D sufficiency as serum 25(OH)D concentration ≥30 ng/mL (≥75 nmol/L) [23,24]. Most literatures have defined 10–15 ng/mL (25–37.5 nmol/l) of 25(OH)D as a cutoff point for vitamin D deficiency for children [4,25–27], which is lower than values reported for adults.

All these determined cutoff values are based on decreased serum 25(OH)D concentration at which serum PTH level starts to rise. However, it is hypothesized that serum 25(OH)D concentration would affect insulin resistance [28]. At present, to the best of our knowledge, there is no published literature that has determined cutoff point of vitamin D deficiency based on serum insulin level or HOMA-IR.

Therefore, this study was designed to determine the cutoff value of vitamin D deficiency based on correlation of 25(OH)D level and insulin resistance. Our secondary objective was to find the prevalence of vitamin D deficiency based on this new cutoff value in children of recruited primary schools of Zanjan province.

2. Materials and methods

2.1. Study population

This cross-sectional study was conducted on 297 healthy school-children aged 7–11 years living in Zanjan, the provincial capital of the same name in the north-western Iran, in the spring and summer of 2011.

All the participants were selected randomly from students of Zanjan branch of SAMA schools, the nationwide private schools under observation of Azad Universities in Iran. The students studying in SAMA schools are representatives of middle to top social class of people living in Zanjan.

The study was approved by the ethical committee of Zanjan University of medical sciences and informed consent was obtained from all the parents of the students.

2.2. Anthropometry and blood pressure measurements

All the participants were examined clinically by trained general practitioners (GPs) for general health. Weight, height and waist circumferences (WC) were measured by standard methods [29] and body mass index (BMI) was calculated and recorded. Blood pressures (BP) were measured three times with 10 min intervals after at least 15 min of rest, and mean of the measurements were considered as BP of the subjects. For those with higher BP the measurement was repeated in other day. NIH charts for normal population were used to define normal values of BP, weight and BMI. Central obesity and hypertension were defined based on levels of WC and BP more than 90th percentile of normal population for each age [30].

2.3. Biochemical measurements

Venous blood samples were collected from the subjects after at least 12 h of fasting. The analysis of samples was performed using Selectra 2 autoanalyzer (Vital scientific, spankeren, Netherlands). Sera were stored at −70 °C until analysis for 25(OH)D, insulin and iPTH. All the measurements were done in one of the laboratory centers approved by Zanjan Metabolic Diseases Research Center for quality of measurements.

Fasting blood sugar (FBS) was measured on the day of blood collection by enzymatic colorimetric method using glucose oxidase. Insulin levels were measured via an electrochemiluminescence immunoassay (ECLIA) using commercially available kits (Roche, German). The homeostasis model assessment index (HOMA index) was used to determine the level of insulin resistance (IR) and was calculated according to the following equation: [insulin (μU/L)] [fasting plasma glucose (FPG) (mmol/L)]/22.5 and considered as marker of insulin resistance when it was more than 2.1 [31]. 25(OH)D levels were assayed by ELISA method using Immunodiagnostic system (IDS) kits with intra- and inter-assay coefficient of variance (CV) 5.3% and 4.6% for lower limit and 6% and 8% for upper limit, respectively. Intact PTH (iPTH) was measured by ELISA method and Biomerica kits with sensitivity of 1.5 pg/mL. Inter- and intra-assay CV for the measurement was 4% and 5%, respectively.

2.4. Statistical analysis

Statistical analysis was conducted with the Statistical Package for the Social Sciences (Version 13; SPSS, Chicago, IL). Normality of the data distribution was assessed with the Kolmogorov–Smirnov test. Results were expressed as mean ± SD and median. Differences in continuous variables between two groups were tested using Student's *t* test or non-parametric Mann–Whitney *U* test, depending on data distribution. The association between serum 25(OH)D and the different study variables were examined by bivariate Pearson or Spearman correlation, depending on data distribution. $p < 0.05$ was considered statistically significant. We determined a cut-off for vitamin D deficiency in our population based on increasing insulin resistance using receiver operating characteristic (ROC) curves.

3. Results

The demographic, clinical, and biochemical characteristics of the study population are summarized in Table 1. Two hundred and ninety seven healthy children [134 (45.2%) boys and 163 (54.8%) girls] aged 7–11 years were enrolled. As shown, no significant differences were found for HOMA-IR between the boys and girls. The mean serum 25(OH)D concentrations and HOMA-IR were 14.1 ± 8.2 ng/mL and 1.83 ± 1.37, respectively.

There was reverse correlation between serum 25(OH)D and HOMA-IR (Spearman's $r = -0.14$, $p = 0.016$; Fig. 1). Using the ROC

Table 1
Demographic and biochemical features of 297 study subjects.

Variables	Boys (n = 134)		Girls (n = 163)		p value	Total (n = 297)	
	Mean ± SD	Median	Mean ± SD	Median		Mean ± SD	Median
Age (years)	7.6 ± 1.3	7	8.4 ± 1.2	8	0.006	7.8 ± 1.3	8
25(OH)D (ng/mL)*	17.62 ± 9.5	15.4	11.20 ± 5.40	10.6	0.000	14.1 ± 8.2	12.6
iPTH (pg/mL)*	33.23 ± 19.97	27.8	50.44 ± 45.67	36.8	0.08	42.67 ± 37.34	30.40
FBS (mg/dL)	82.45 ± 12.12	83.0	83.08 ± 9.88	84.00	0.925	82.79 ± 10.93	83.00
Insulin (μu/L)*	8.63 ± 7.48	6.60	9.23 ± 6.41	7.70	0.086	8.96 ± 6.90	7.00
HOMA-IR*	1.74 ± 1.37	1.36	1.90 ± 1.36	1.52	0.163	1.83 ± 1.37	1.43

n = number; HOMA-IR, homeostatic model assessment for insulin resistance; FBS, fasting blood sugar; 25(OH)D, 25-hydroxy vitamin D; iPTH, intact parathyroid hormone.
* p value was calculated by the independent t-test or by the non-parametric Mann–Whitney U-test; a p value <0.05 was considered significant.