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Evaluation of the Correlation Between Vitamin D Level and Insulin Resistance in Children with Overweight and Obesity

Fazla Kilolu ve Obeziteli Çocuklarda D Vitamini Düzeyi ile İnsülin Direnci Arasındaki Korelasyonunun Değerlendirilmesi

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ABSTRACT

Aim: This study aimed to evaluate the relationship between vitamin D levels and insulin resistance parameters in children with overweight and obesity.
Material and Methods: A total of 174 children, 64.4% (n=112) female, and 35.6% (n=62) male, aged between 6-17 years were included in the study. The participants were divided into three groups as normal (29.9%, n=52), overweight (23.6%, n=41), and obesity (46.5%, n=81) based on the criteria of the World Health Organization body mass index (BMI) classification. The insulin resistance status of the participants was evaluated by homeostatic model assessment of insulin resistance (HOMA-IR), fasting glucose to insulin ratio (FGIR), and quantitative insulin sensitivity check index (QUICKI).
Results: HOMA-IR was found higher in the obesity group (3.2±2.1) compared to the overweight (2.2±1.0) and the normal weight (1.5±1.0) groups (p<0.001). It was observed that QUICKI values of the overweight (0.34±0.03) and the obesity (0.33±0.03) groups were lower than the normal weight (0.37±0.03) group (p<0.001). FGIR was noticed as higher in the normal weight (16.8±10.4) group compared to the overweight (10.6±6.0) and the obesity (8.5±5.5) groups (p<0.001). The mean serum 25-hydroxyvitamin D [25(OH)D] levels of the children and adolescents were 19.6±10.7 ng/mL, and no statistically significant difference was found between the groups (p=0.153). A significant weak negative correlation between serum 25(OH)D and HOMA-IR values was found (r=-0.170, p=0.025). Additionally, a weak positive statistically significant correlation was found between serum 25(OH)D level and QUICKI and FGIR values (r=0.173, p=0.022, and r=0.173, p=0.023, respectively).
Conclusion: Vitamin D levels can affect insulin resistance parameters.
Keywords: Insulin resistance; pediatric obesity; vitamin D.

ÖZ

Amaç: Bu çalışmada fazla kilo ve obezitesi olan çocuklarda D vitamini düzeyleri ile insülin direnci parametreleri arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntemler: Çalışmaya 6-17 yaş aralığında, %64,4% (n=112) kız ve %35,6 (n=62) erkek, toplam 174 çocuk dahil edilmiştir. Katılımcılar, Dünya Sağlık Örgütü beden kitle indeksi (BKİ) sınıflaması kriterlerine göre normal (%29,9; n=52), fazla kilolu (%23,6; n=41) ve obezite (%46,5; n=81) olmak üzere üç gruba ayrılmıştır. Katılımcıların insülin direnci durumları, insülin direncinin homeostatik model değerlendirmesi (homeostatic model assessment of insulin resistance, HOMA-IR), açlık glikozunun insüline oranı (fasting glucose to insulin ratio, FGIR) ve kantitatif insülin duyarlılığı kontrol indeksi (quantitative insulin sensitivity check index, QUICKI) ile değerlendirilmiştir.
Bulgular: HOMA-IR, fazla kilolu (2,2±1,0) ve normal kilolu (1,5±1,0) gruplara göre obezite grubunda (3,2±2,1) yüksek bulunmuştur (p<0,001). Fazla kilolu (0,34±0,03) ve obezite (0,33±0,03) gruplarının QUICKI değerlerinin normal kilolu (0,37±0,03) gruptan daha düşük olduğu görülmüştür (p<0,001). FGIR, normal kilolu grupta (16,8±10,4), fazla kilolu (10,6±6,0) ve obezite (8,5±5,5) gruplarına göre daha yüksek saptanmıştır (p<0,001). Çocuk ve adölesanların ortalama serum 25-hidroksivitamin D [25(OH)D] düzeyi 19,6±10,7 ng/mL olup, gruplar arasında istatistiksel olarak anlamlı bir farklılık bulunmamıştır (p=0,153). Serum 25(OH)D ile HOMA-IR değerleri arasında anlamlı, zayıf negatif (r=-0,170; p=0,025) bir korelasyon bulunmuştur. Buna ek olarak, serum 25(OH)D düzeyi ile QUICKI ve FGIR değerleri arasında zayıf pozitif istatistiksel olarak anlamlı (sırasıyla, r=0,173; p=0,022 ve r=0,173, p=0,023) bir korelasyon bulunmuştur.
Sonuç: D vitamini düzeyleri insülin direnci parametrelerini etkileyebilir.
Anahtar kelimeler: İnsülin direnci; pediatrik obezite; D vitamini.

INTRODUCTION

Insulin resistance, one of the complications of increasing body weight, can be seen widely in childhood, parallel with the increase in obesity frequency (1). Insulin resistance is a disorder that affects many organ systems and causes significant metabolic damage (2). Multiple factors, including various genetic, environmental, and biochemical reasons, influence the development of insulin resistance. Additionally, dietary patterns (especially diets with a high saturated fatty acid, sucrose, and energy content) increase hepatic insulin resistance and free oxygen species formation. The risk of developing insulin resistance reduces with preventive measures and therapeutic interventions, so it is crucial to define environmental factors. In this context, the most critical risk factors are low physical activity level, weight gain, obesity, and unhealthy nutrition habits. These factors can impair or alter insulin sensitivity (3,4). Besides, vitamin D, which involves in the function of insulin-sensitive tissues, including the liver and skeletal muscle, and has potential effects on the regulation of insulin secretion and the survival of pancreatic beta cells, may play a role in the pathogenesis of insulin resistance (5-7). However, the contradictory results of the studies (8-10) necessitate the evaluation of the relationship between vitamin D levels and insulin resistance in childhood. Based on the study results, a more explicit demonstration of the association between vitamin D deficiency and insufficiency and the risk of developing insulin resistance may be an effective strategy to fight against insulin resistance (7,11).

This study aimed to evaluate the relationship between insulin resistance and vitamin D levels in children and adolescents with overweight and obesity aged 6-17.

MATERIAL AND METHODS

This cross-sectional study was conducted with 174 children and adolescents (ages 6-17) who were admitted to the Gülhane Training and Research Hospital Pediatric Endocrine Department between August to December 2019. Those who regularly used any nutritional supplements (vitamin D, iron, fish oil, prebiotics, probiotics, etc.) in the last three months, those with perception and communication problems, those with thinness, chronic diseases, and growth retardation, were not included in this study.

To conduct the study, Ethics Committee Approval dated 18 July 2019 and Decision No: İ2-32-19 from Ankara University Ethics Committee and Research Permission dated 28 August 2019 from the Gülhane Training and Research Hospital, where the data will be collected, were obtained. Before the data started to be collected, the participants and their parents were informed about the research, and the purpose was explained. Those who agreed to participate and those with parental consent were included in the study. Also, each participant signed the informed volunteer consent form.

The dieticians measured height and body weight, and the body mass index (BMI) of the participants was calculated with the formula, weight (kg)/height^2 (m^2). BMI values were evaluated according to the growth standards determined by the WHO for 5-19 years old. BMI was categorized as follows: -1SD≥BMI≤+1SD indicating normal weight, +1SD>BMI≤2SD indicating overweight, and BMI>2SD indicating obesity (12). WHO Antroplus program was used to determine the BMI z-scores of the participants (13). Some biochemical parameters, fasting blood glucose, serum 25-hydroxyvitamin D [25(OH)D], and fasting insulin checked in the last three months were obtained from the patient folders and evaluated by the pediatric endocrinologists.

The status of insulin resistance in participants was determined using homeostatic model assessment of insulin resistance (HOMA-IR) calculated by the formula fasting insulin (uIU/mL) × fasting blood glucose (mg/dL) / 405, fasting glucose to insulin ratio (FGIR), and quantitative insulin sensitivity check index (QUICKI) (14). There is no standard value for HOMA-IR to define insulin resistance in children and adolescents, and different cut-off values are referenced in different populations (15). In this study, HOMA-IR reference values for Turkish children and adolescents (5-18 years) were used. The HOMA-IR reference values in the prepubertal period, ≥2.67 in males and ≥2.22 in females; and in the pubertal period, ≥5.22 in males and ≥3.82 in females, were defined as insulin resistance (16). FGIR value <7 was considered insulin resistance (17). QUICKI was calculated with the formula: 1 / [log (fasting insulin (uIU/mL)) + log (fasting glucose (mg/dL))] (14). QUICKI value <0.34 was defined as insulin resistance (18). Serum 25(OH)D level was categorized as follows, deficiency: <12 ng/mL, insufficiency: 12-20 ng/mL, and normal: >20 ng/mL (19).

Statistical Analysis

The data were evaluated with IBM SPSS v.26.0 for Windows. Basic descriptive statistics (frequency, percentage, mean, standard deviation, median, interquartile range, minimum, and maximum) were used. The chi-square test was used to compare categorical variables. Normality was examined using the Kolmogorov-Smirnov test. While comparing more than two groups, the one-way analysis of variance (ANOVA) was used under normal distribution assumptions, and the Kruskal-Wallis test was used when not. Bonferroni test was used to determine from which group the difference originated for ANOVA and in case the Kruskal-Wallis test, the Bonferroni corrected Mann-Whitney U test was applied as a post hoc test. Pearson or Spearman correlation analysis was used to evaluate the correlation between the quantitative variables according to the normality assumptions. A p value of <0.05 was considered as statistical significance.

RESULTS

The study was conducted with 174 children (35.6% (n=62) male, and 64.4% (n=112) female) with a mean age of 11.6±3.17 years. In accordance with BMI z-scores, 46.5% (n=81) of the children were with obesity, while 23.6% (n=41) were overweight, and 29.9% (n=52) were normal weight. There was no statistically significant difference between the BMI groups in regard to general characteristics (Table 1).

The participants' mean fasting blood glucose level was 88.2±7.79 mg/dL, and no significant difference was found between the BMI groups (p=0.974). Participants with normal weight had lower mean fasting insulin levels compared to overweight and obesity groups (p<0.001).

HOMA-IR value was found to be higher in the obesity group compared to the overweight and the normal weight groups (p<0.001). The QUICKI value was higher in participants with normal weight compared to the overweight and the obesity groups (p<0.001). Similarly, the FGIR value was higher in children with normal weight compared to the overweight and obesity groups (p<0.001). The participants' mean serum 25(OH)D level was 19.6±10.7 ng/mL. Additionally, no significant difference was found between the BMI groups (p=0.153, Table 2).

According to the HOMA-IR classification, 5.8% (n=3) of the participants with normal weight, 9.8% (n=4) of the participants with overweight, and 37.0% (n=30) of the participants with obesity had insulin resistance. Compared to the children with normal weight, insulin resistance prevalence was higher in children with overweight and obesity (p<0.001, Table 3).

Vitamin D was deficient in 22.4% (n=39) and was insufficient in 39.1% (n=68) of children and adolescents participating in the study. These values were 28.8% (n=15) and 34.6% (n=18), respectively, in children with normal weight. While the ratios of those who were deficient and insufficient in terms of vitamin D levels in the overweight group were 9.8% (n=4), and 48.8% (n=20), these ratios were 24.7% (n=20) and 37.0% (n=30), respectively, among the obesity group. No statistically significant difference was found between the BMI groups in terms of the distribution of 25(OH)D levels (p=0.234, Table 3).

Table 1. Demographic characteristics of participants according to the BMI groups

	Normal (n=52)	Overweight (n=41)	Obesity (n=81)	p	Total (n=174)
Gender, n (%)					
Male	14 (26.9)	12 (29.3)	36 (44.4)	0.750	62 (35.6)
Female	38 (73.1)	29 (70.7)	45 (55.6)		112 (64.4)
Age groups, n (%)					
6-9 years	19 (36.5)	11 (26.8)	19 (23.5)	0.256	49 (28.2)
10-17 years	33 (63.5)	30 (73.2)	62 (76.5)		125 (71.8)
Age (year), mean±SD	11.2±3.2	12.4±3.4	11.6±3.0		11.6±3.2
median (IQR) [min-max]	11 (5.8) [6-17]	12 (7) [6-17]	11 (4) [6-17]	0.192	11 (5) [6-17]

BMI: body mass index, SD: standard deviation, IQR: interquartile range

Table 2. Comparison of biochemical findings, insulin resistance, and serum 25(OH)D levels

	Normal (n=52)	Overweight (n=41)	Obesity (n=81)	p	Total (n=174)
Glucose (mg/dL)	88.0±8.4 87.5 (9.0) [63-111]	88.3±8.0 87.0 (7.5) [63-115]	88.2±7.4 87.0 (11.0) [73-106]	0.974	88.2±7.8 87.0 (9.0) [63-115]
Insulin (uIU/mL)	7.0±4.2[a] 6.4 (4.8) [1.3-26.6]	10.2±4.2[b] 10.1 (6.3) [2.2-18.6]	14.4±8.8[c] 12.2 (9.6) [2.9-48.0]	**<0.001**	11.2±7.5 9.5 (8.5) [1.3-48.0]
HOMA-IR	1.5±1.0[a] 1.4 (1.1) [0.3-6.1]	2.2±1.0[b] 2.1 (1.5) [0.4-4.9]	3.2±2.1[c] 2.7 (2.4) [0.6-11.3]	**<0.001**	2.5±1.8 2.1 (1.9) [0.3-11.3]
QUICKI	0.37±0.03[a] 0.36 (0.05) [0.29-0.50]	0.34±0.03[b] 0.34 (0.04) [0.30-0.44]	0.33±0.03[b] 0.32 (0.04) [0.27-0.42]	**<0.001**	0.34±0.04 0.34 (0.04) [0.27-0.50]
FGIR	16.8±10.4[a] 13.6 (9.9) [3.5-58.2]	10.6±6.0[b] 8.9 (4.9) [4.6-36.9]	8.5±5.5[b] 6.9 (4.9) [1.9-29.3]	**<0.001**	11.5±8.2 9.2 (7.4) [1.9-58.2]
25(OH)D (ng/mL)	19.8±13.4 16.8 (15.4) [4.9-64.6]	21.8±10.3 18.9 (10.5) [5.9-52.2]	18.3±8.8 17.1 (10.7) [4.9-40.9]	0.153	19.6±10.7 17.6 (11.7) [4.9-64.6]

25(OH)D: 25-hydroxyvitamin D, HOMA-IR: homeostatic model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index, FGIR: fasting glucose to insulin ratio, [a,b,c]: each different superscript letter denotes significant differences between groups, mean±standard deviation and median (interquartile range) [min-max]

Table 3. Distribution of participants according to the insulin resistance parameters and 25(OH)D levels

	Normal (n=52)	Overweight (n=41)	Obesity (n=81)	p	Total (n=174)
HOMA-IR, n (%)					
Suboptimal	3 (5.8)[a]	4 (9.8)[a]	30 (37.0)[b]	**<0.001**	37 (21.3)
Optimal	49 (94.2)[a]	37 (90.2)[a]	51 (63.0)[b]		137 (78.7)
QUICKI, n (%)					
<0.34	7 (13.5)[a]	19 (46.3)[b]	51 (63.0)[b]	**<0.001**	77 (44.3)
≥0.34	45 (86.5)[a]	22 (53.7)[b]	30 (37.0)[b]		97 (55.7)
FGIR, n (%)					
<7	3 (5.8)[a]	12 (29.3)[b]	42 (51.9)[b]	**<0.001**	57 (32.8)
≥7	49 (94.2)[a]	29 (70.7)[b]	39 (48.1)[b]		117 (67.2)
25(OH)D, n (%)					
Deficient	15 (28.8)	4 (9.8)	20 (24.7)	0.234	39 (22.4)
Insufficient	18 (34.6)	20 (48.8)	30 (37.0)		68 (39.1)
Normal	19 (36.6)	17 (41.4)	31 (38.3)		67 (38.5)

25(OH)D: 25-hydroxyvitamin D, HOMA-IR: homeostatic model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index, FGIR: fasting glucose to insulin ratio, [a,b]: each different superscript letter denotes significant differences between groups

Of the participants with insulin resistance according to the HOMA-IR value, 21.6% (n=8) were vitamin D deficient, 37.8% (n=14) were insufficient, and 40.6% (n=15) were normal. No significant difference was determined between the distribution of 25(OH)D levels of the participants according to insulin resistance status (p=0.960, Table 4).
A weak negative correlation was determined between HOMA-IR and 25(OH)D levels (r=-0.170, p=0.025). A weak positive correlation was determined between serum 25(OH)D and QUICKI (r=0.173, p=0.022), and between serum 25(OH)D and FGIR (r=0.173, p=0.023, Table 5).

DISCUSSION

Obesity is the most crucial risk factor for insulin resistance and type 2 diabetes. Nevertheless, diabetes may not develop in every individual with obesity and insulin resistance. In the absence of functional impairment in the beta cells of the pancreas, insulin resistance in individuals with obesity without diabetes can be compensated by increasing insulin levels. Increased insulin levels in patients with obesity compared to normal-weight individuals may compensate for the decreased insulin effect, resulting in glucose levels similar to normal-weight individuals (20). In this study, the similarity in blood glucose levels of children with normal weight, overweight, and obesity can be explained by the fact that they did not have type 2 diabetes, and those with insulin resistance were in the asymptomatic stages.
In this study, the mean fasting insulin level of participants with normal weight was lower compared to the overweight and obesity groups. In Düzce, a study with similar results was also found (21). A study conducted in Denmark found that as body weight increases, fasting insulin level also increases (22). Various mechanisms in obesity may cause the development of hyperinsulinemia, such as dysregulation of lipid and glucose metabolism, hormone imbalance, and inflammation (23). These reasons may explain the higher insulin levels in individuals with obesity.
According to the results of this study, insulin resistance was more common in children with obesity (37.0%) compared to those with overweight (9.8%) and with normal weight (5.8%), and this result is consistent with the literature (24,25). In other words, the HOMA-IR value was higher in the obesity group (3.2±2.1) compared to the overweight group (2.2±1.0) and normal weight group (1.5±1.0). QUICKI value was higher in participants with normal weight (0.37±0.03) compared to those with overweight (0.34±0.03) and with obesity (0.33±0.03). Similarly, the FGIR value was higher in the normal weight group (16.8±10.4) compared to the overweight (10.6±6.0) and obesity groups (8.5±5.5). In a study conducted in Ankara, the mean HOMA-IR value of 164 children with overweight and obesity between the ages of 9-13 was determined to be 4.7±2.7, and insulin resistance was found in 62.2% of the participants (26). In another study conducted with children with obesity in Ankara, the mean HOMA-IR value was found 3.3±2.8, and the frequency of insulin resistance was 44.4% (27). Changes in adipose tissue secretions such as increased free fatty acids and leptin levels and decreased adiponectin levels in obesity cause insulin resistance development (20). Also, increased secretion of pro-inflammatory cytokines (IL-6, TNF-α) plays a role in developing insulin resistance (28). For these reasons, the connection between obesity and insulin resistance is not surprising. However, it should be noted that standard methods are needed to evaluate the prevalence of insulin resistance in children (29). According to countries, ages, and gender, different parameters and cut-off points can be used to diagnose insulin resistance. Even in the same region, various cut-off points are used in several studies (15). In this study, too, insulin resistance was evaluated based on the HOMA-IR, FGIR, and QUICKI index, and different results were obtained. Therefore, it is difficult to get exact data on the prevalence of insulin resistance in childhood and compare it based on age, gender, body weight, and country.
The mean serum 25(OH)D levels of children and adolescents were 19.6±10.7 ng/mL and were insufficient. In general, vitamin D level was deficient in 22.4% of the participants, insufficient in 39.1%, and normal in 38.5%. No significant difference was found between normal weight, overweight, and obesity groups in terms of serum

Table 4. Distribution of vitamin D levels of participants by the status of insulin resistance

	HOMA-IR		p	QUICKI		p	FGIR		p
	IR+ (n=37)	IR- (n=137)		IR+ (n=77)	IR- (n=97)		IR+ (n=57)	IR- (n=117)	
25(OH)D, n (%)									
Deficient	8 (21.6)	31 (22.6)		21 (27.3)	18 (18.6)		15 (26.3)	24 (20.5)	
Insufficient	14 (37.8)	54 (39.4)	0.960	32 (41.5)	36 (37.1)	0.165	24 (42.1)	44 (37.6)	0.400
Normal	15 (40.6)	52 (38.0)		24 (31.2)	43 (44.3)		18 (31.6)	49 (41.9)	

25(OH)D: 25-hydroxyvitamin D, HOMA-IR: homeostatic model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index, FGIR: fasting glucose to insulin ratio, IR: insulin resistance

Table 5. Correlation of serum 25(OH)D level and insulin resistance parameters

	Normal (n=52)		Overweight (n=41)		Obesity (n=81)		Total (n=174)	
	r_s	p	r	p	r	p	r_s	p
HOMA-IR	-0.178	0.206	-0.024	0.881	-0.249	**0.025**	-0.170	**0.025**
QUICKI	0.179	0.203	-0.009	0.954	0.272	**0.014**	0.173	**0.022**
FGIR	0.223	0.112	0.039	0.806	0.266	**0.017**	0.173	**0.023**

25(OH)D: 25-hydroxyvitamin D, HOMA-IR: homeostatic model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index, FGIR: fasting glucose to insulin ratio, r: Pearson correlation coefficient, r_s: Spearman's rho

25(OH)D level distribution. A study conducted with a large population (14473 participants) between the ages of 6-17 years in China found that the serum vitamin D levels did not differ significantly according to the BMI classification (30). A study in Istanbul found that 9.0% of the children were in vitamin D deficiency, and 22.9% in vitamin D insufficiency (31). In another study conducted with 640 children in the 6-9 age group in Istanbul, the frequency of vitamin D deficiency was 5.62%, and the insufficiency was 18.6% (32). The studies conducted in different countries also show that vitamin D deficiency is common in children and adolescents (30,33-36). There are a variety of reasons why vitamin D deficiency is common. A limited number of foods such as salmon, mackerel, eggs, and liver naturally contain vitamin D. Inadequate consumption of foods containing vitamin D may play a role in its deficiency. Inadequate sun exposure, reduced outdoor activities, clothing style, intensive use of sunscreens, air pollution, and physiological factors such as dark skin pigmentation, malabsorption syndromes, and hepatic/renal failure may also cause vitamin D deficiency (37). The common prevalence of vitamin D deficiency and insufficiency in this study may be due to the study being conducted in a wide season range, including autumn and winter. Because the weather is cold and overcast, the children reduced their time outdoors, which caused them to not benefit from sunlight, which is the primary vitamin D synthesis source.

This study did not show a significant difference between the distribution of 25(OH)D levels according to the insulin resistance status. However, the decrease in vitamin D levels was significantly associated with an increase in HOMA-IR values and decreased QUICKI and FGIR values. The studies conducted with children and adolescents in different countries also support this result (38,39). Various mechanisms play a role in the relationship between vitamin D and insulin metabolism. Since pancreatic β-cells express the vitamin D receptor, vitamin D seems to be required for proper insulin secretion. Increasing insulin sensitivity, inhibiting inflammatory factors, and reducing the chronic inflammation process of the pancreas are all possible outcomes of combining calcitriol with the vitamin D receptor on islet β cells. This ultimately leads to an improvement in the function of islet β cells. Additionally, vitamin D may reduce hyperactivity of the renin-angiotensin system and improve the function of β-cells. In addition to this, vitamin D may alter insulin release mediated by calcium channel opening and closing (40,41).

This study had potential limitations. Vitamin D insufficiency and deficiency were frequent in children in the study may be due to the wide season period, which includes cold and rainy months. In future studies, it is recommended to limit the season period and evaluate the sun exposure of the participants (such as outdoor time, playing, and outdoor sports activities). This study did not assess vitamin D intake via the food of participants because of the lack of products enriched with vitamin D in Turkey and insufficient vitamin D intake through diet (8). Also, Tanner's stage of puberty and sex hormones were not assessed in the participants. In future studies, it is recommended to consider this situation, and it will be useful to make plans according to countries.

CONCLUSION

In this study, the insufficiency or deficiency of serum vitamin D levels in most children and adolescents indicates that outdoor activities should be increased, especially in school health programs. Additionally, finding a relation between serum vitamin D levels and insulin resistance parameters suggests that vitamin D may have a role in the pathogenesis of insulin resistance. In this context, to better understand the role of vitamin D on insulin resistance, it is recommended to conduct comprehensive studies that take into account the other factors that may affect vitamin D function, for instance, the physical (season, clothing style), and the biochemical parameters (calcium, parathyroid hormone).

Ethics Committee Approval: The study was approved by the Ethics Committee of Ankara University Human Research Ethics Committee (18.07.2019, İ2-32-19).

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