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ORIGINAL ARTICLE

Serum Vitamin D, Zinc Levels and the Relationship between them in Children and Adolescents

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SUMMARY

Background: **Along with vitamin D deficiency, a common global health problem in developed and developing countries, zinc deficiency also remains one of the most common micronutrient deficiencies-related public health problems in some parts of the world. Determination of vitamin D and Zn status is important for the growth, development, and health of school-age children, as well as their intellectual achievement and academic performance. In this study, we aimed to evaluate serum 25(OH)D and Zn levels and the relationship between them in a nationally representative sample of Turkish children and adolescents.**
Methods: **A total of 541 children and adolescents aged 1 - 16 years were included in our study whose vitamin D and zinc test levels were measured and who applied to the Basaksehir Cam and Sakura City Hospital Pediatric Outpatient Clinic. Cases were examined by dividing them into subgroups according to their vitamin D levels (≤ 15 ng/mL deficiency; 15 - 20 ng/mL insufficiency; ≥ 20 ng/mL sufficiency) and age (< 5 years preschool; 5 - 10 years middle childhood; 11 - 16 years adolescence).**
Results: **The levels of 25(OH)D were lower than 20 ng/mL in 33% of the children. There was deficiency in 80 (15%) and insufficiency in 99 (18%) cases. A statistically significant difference was found in 25(OH)D and Zn levels in groups separated by 25(OH)D level and age ($p < 0.001$). A positive significant correlation was found between serum 25(OH)D and Zn levels ($r = 0.468$; $p < 0.001$). A negative correlation was found between 25(OH) D levels and age ($r = -0.261$; $p < 0.001$) and body mass index (BMI) ($r = -0.308$; $p < 0.001$).**
Conclusions: **In our study, we found high levels of vitamin D deficiency and insufficiency and a significant positive correlation between serum 25(OH)D and Zn levels in the pediatric population. Based on this possible contribution, we think that providing vitamin D support to children of all ages, including adolescents, and thus improving zinc levels may be beneficial in protecting from diseases that lead to morbidity and mortality as a result of reducing the rate of growth and development retardation, regulating of bone development, and contributing to the development of the immune system.**
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INTRODUCTION

Vitamin D insufficiency is an important global public health problem with a high prevalence in developed countries as well as developing countries [1]. Lifestyle changes, obesity "outbreaks", and various preventable risk factors have led to the reappearance of vitamin D deficiency in childhood in developed countries [2]. Vitamin D is a prohormone that plays an important role in calcium and phosphorus metabolism and is an important determinant of bone health. Animal and human studies have shown that vitamin D is also important for normal brain development [3]. In addition, since many cells express vitamin D receptors, vitamin D has also been shown to have effects on non-skeletal tissues in enhancing immune function and reducing inflammation [2].

In some studies, an association has been found between vitamin D deficiency with acute and chronic diseases such as cardiovascular disease, type 1 diabetes mellitus, schizophrenia, depression, Alzheimer's disease, various malignancies, systemic lupus erythematosus, multiple sclerosis, infectious diseases, and atopy [4]. It has been shown that children diagnosed with Attention-Deficit/ Hyperactivity Disorder (ADHD), which is an important problem in childhood, have lower levels 25-OH vitamin D levels [5]. Inadequate dietary vitamin D intake, lifestyle habits, insufficient sunlight exposure, genetic polymorphisms, ethnicity, obesity, dark skin color, living at high latitudes, malabsorption syndromes, chronic drug use may cause vitamin D deficiency in children. Cholecalciferol and ergocalciferol are biologically inactive. It is converted to 25(OH)D stored in the liver and body fat [6]. Due to its 2- to 3-week half-life, serum 25(OH)D level measurement is widely used to establish vitamin D status in the body [7].

Studies have been conducted showing the relationship between 25(OH)D levels and serum levels of various vitamins and elements [8]. Calcium, magnesium, iron, zinc, and copper are some of the elements that play an important role in physiological and chemical functions in the body. Zinc is the second most common trace element in the human body, which is involved in the structure of about 300 enzymes needed for growth development, bone structure, immune system, wound healing, catalytic reactions, and collagen synthesis [9]. The vast majority of zinc is found in bone, skeletal muscle, and skin, not stored. Of the total amount of zinc in the body, 0.1% is in plasma [10]. Zn deficiency affects both developed and developing countries [11]. Since zinc is involved in many basic physiological functions in the body, its deficiency can cause serious complications such as growth and developmental retardation, suppression of the immune system, hypogonadism, hepatosplenomegaly, hair loss, dermatitis, diarrhea, infections, depression, premature rupture of membranes in pregnancy, low birth weight, prematurity, neuraltube defects in the fetus, and cleft palate [3]. Moreover, zinc deficiency is estimated to be responsible for 4% of child deaths and diseases worldwide [11]. In some studies, it has been stated that there is a statistically significant relationship between serum 25(OH)D and zinc levels [8]. Along with vitamin D deficiency, zinc deficiency remains one of the most common micronutrient deficiencies-related public health problems in some parts of the world. Determination of vitamin D and Zn status is important for their intellectual achievements and academic performance, as well as for the growth, development, and health of school-age children. Both the high prevalence of vitamin D deficiency and its interaction with other vitamins and elements have led to an increase in the importance of supportive therapy with the early detection of vitamin D deficiency. There are not enough studies on the relationship between serum 25(OH)D concentrations and Zn. Therefore, the aim of this study is to evaluate the frequency of vitamin D deficiency and insufficiency and the relationship between serum vitamin D and zinc levels in the Turkish child-adolescent sample, considering the prevalence and possible interactions of vitamin D and zinc deficiency.

MATERIALS AND METHODS

Study design and participants

The study was approved by the ethics committee of Ordu University Faculty of Medicine (Date: 26.11.20 No.: 2020/278). Due to the retrospective and observational character of the studydesign, the requirement for informed consent has been waived.

This study was conducted with 541 children and adolescents in Istanbul Basaksehir Cam and Sakura City Hospital. All children and adolescents aged 1 - 16 years, who were examined in the Pediatric outpatient clinic between September 1 and November 30, 2020, whose vitamin D and zinc levels were determined and whose data could be accessed were included in this retrospective study. Those with chronic diseases or those using vitamin D and Zn supplements were not included in the study. Cases were divided into 3 groups according to their vitamin D levels ($\leq$ 15 ng/mL deficiency (group 1), 15 - 20 ng/mL insufficiency (group 2), and $\geq$ 20 ng/mL sufficiency (group 3)) [12]. In addition, they were divided into 3 groups according to their age (< 5 years preschool (group 1), 5 - 10 years middle childhood (group 2), and 11 - 16 years adolescence (group 3)). The cases were compared according to their vitamin D levels and age groups.

Data collection and analysis

Age, gender, BMI, vitamin D, and zinc data were analyzed retrospectively through the hospital information system and compared. All tests were analyzed in the Central Laboratory of Basaksehir Cam and Sakura City Hospital. The tests were performed with serum obtained from venous blood samples taken into gel tubes for biochemical parameters and NH trace elements sodium heparin tube for Zn.

Serum glucose, urea, creatinine, and lipid profile were measured with the enzymatic colorimetric method, and serum 25(OH)D levels with the electrochemiluminescence method in Roche Cobas 8000 (Roche Indianapolis/America) analyzer. Serum Zn levels were measured using Archem ZINC kit with Flame atomic absorption

Table 1. Metabolic data of groups formed according to vitamin D levels.

	Group 1 (n = 80) M ± IQR (Min - Max)	Group 2 (n = 99) M ± IQR (Min - Max)	Group 3 (n = 362) M ± IQR (Min - Max)	p *
Age, years	9 ± 9 (1 - 18)	7 ± 6 (1 - 17)	6 ± 4 (1 - 18)	< 0.001
BMI (kg/m²)	18.8 ± 4.6 (10.9 - 31.0)	17.2 ± 4.8 (11.8 - 31.8)	16 ± 2.8 (11.4 - 28.7)	< 0.001
25(OH)D (ng/mL)	11 ± 4.8 (3 - 15)	18 ± 2 (16 - 19)	31 ± 10 (20 - 85)	< 0.001
Zinc (µg/L)	873 ± 189.3 (555 - 1,185)	909 ± 122 (631 - 1,112)	967 ± 142 (645 - 1,408)	< 0.001
Glucose (mg/dL)	90 ± 10 (70 - 267)	90 ± 11.8 (69 - 237)	89 ± 11 (28 - 308)	0.137
Urea (mg/dL)	22 ± 8.5 (11 - 55)	23 ± 10 (9 - 45)	26 ± 12 (10 - 53)	< 0.001
Creatinine (mg/dL)	0.4 ± 0.23 (0.07 - 0.78)	0.39 ± 0.16 (0.00 - 10.40)	0.39 ± 0.13 (0.15 - 39)	0.005
Triglycerides (mg/dL)	78 ± 51.5 (31 - 1,334)	67 ± 57 (28 - 251)	58 ± 33 (25 - 232)	< 0.001
Cholesterol (mg/dL)	152 ± 35 (50 - 308)	155 ± 31 (92 - 282)	168 ± 47 (33 - 435)	< 0.001
HDL (mg/dL)	58 ± 19.5 (8 - 93)	53 ± 20.5 (18 - 104)	59 ± 18 (27 - 123)	< 0.001

M - median, IQR - Interquartile range, Mi - minimum value, Max - maximum value.
*** Kruskal-Wallis.**

Table 2. Metabolic data of groups formed according to age.

	Preschoolgroup (n = 173) M ± IQR (Min - Max)	Middle childhoodgroup (n = 262) M ± IQR (Min - Max)	Adolescence group (n = 106) M ± IQR (Min - Max)	p *
Age, years	3 ± 2 (1 - 6)	7 ± 2 (5 - 10)	13.5 ± 3.25 (11 - 18)	< 0.001
BMI (kg/m²)	15.8 ± 2.9 (10.9 - 28.7)	16.4 ± 3.1 (11.4 - 28.9)	19 ± 4.5 (12.2 - 31.8)	< 0.001
25(OH)D (ng/mL)	29 ± 16.5 (10 - 73)	26 ± 13 (6 - 85)	19 ± 16 (3 - 68)	< 0.001
Zinc (µg/L)	952 ± 173 (606 - 1,381)	956 ± 126 (555 - 1,408)	916 ± 146 (593 - 1,321)	0.025
Glucose (mg/dL)	86 ± 12 (56 - 128)	90 ± 10 (28 - 237)	93 ± 8 (74 - 308)	< 0.001
Urea (mg/dL)	25 ± 11 (9 - 50)	26 ± 11 (10 - 55)	21 ± 10.8 (10 - 43)	< 0.001
Creatinine (mg/dL)	0.32 ± 0.09 (0.00 - 39)	0.41 ± 0.10 (0.23 - 10.40)	0.55 ± 0.16 (0.07 - 0.89)	< 0.001
Triglycerides (mg/dL)	60 ± 36 (25 - 284)	57 ± 30 (28 - 244)	84 ± 47 (28 - 1,334)	< 0.001
Cholesterol (mg/dL)	163 ± 40 (84 - 397)	164 ± 48.3 (33 - 435)	158 ± 41 (92 - 308)	< 0.001
HDL (mg/dL)	56.5 ± 78 (8 - 103)	62 ± 17.8 (20 - 96)	52.5 ± 17.8 (20 - 96)	< 0.001

M - median, IQ - Interquartile range, Min - minimum value, Max - maximum value.
*** Kruskal-Wallis test.**

method in Shimadzu AA-7000 (Shimadzu AA- 7000, Kyoto/Japan) device.

Statistical analysis

A one-way ANOVA with Bonferroni multiple comparison tests was used for the quantitative data analysis. Values for descriptive statistical analyses were expressed as median, interquartile range, minimum and maximum values. Whether the groups showed normal distribution was evaluated with the Kolmogorov-Smirnov test. Kruskal-Wallis and Mann-Whitney U tests were used to compare variables that did not have a normal distribution. Pearson's chi-squared and Fisher's exact tests were used to compare categorical variables. The relationship between the variables was evaluated with the Spearman's correlation coefficient. $p < 0.05$ was accepted for statistical significance. "IBM SPSS Statistics version 24.0" statistical program was used for statistical analysis.

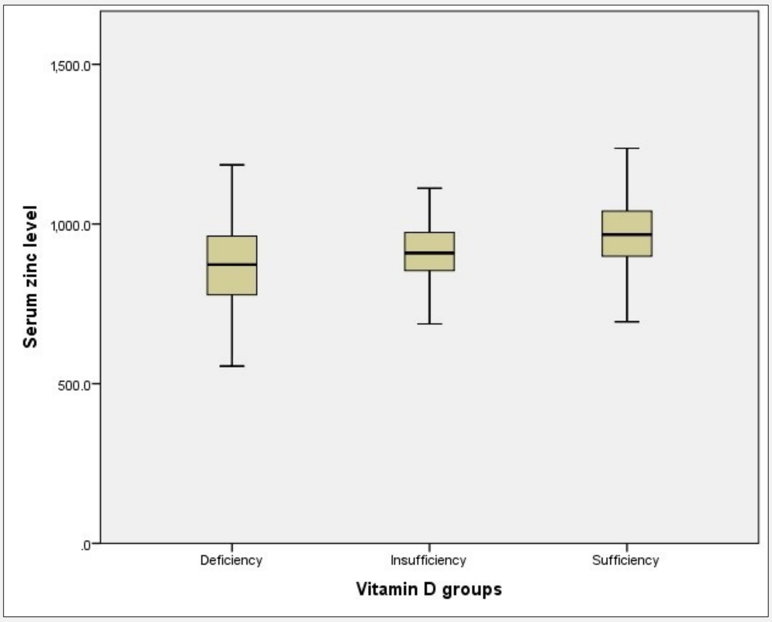

Figure 1. Serum zinc levels according to vitamin D levels.

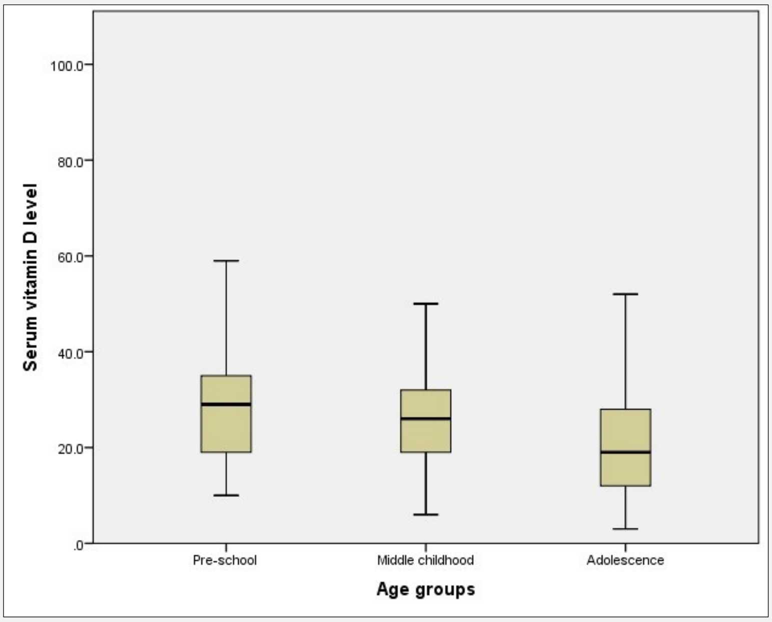

Figure 2. Vitamin D levels according to age.

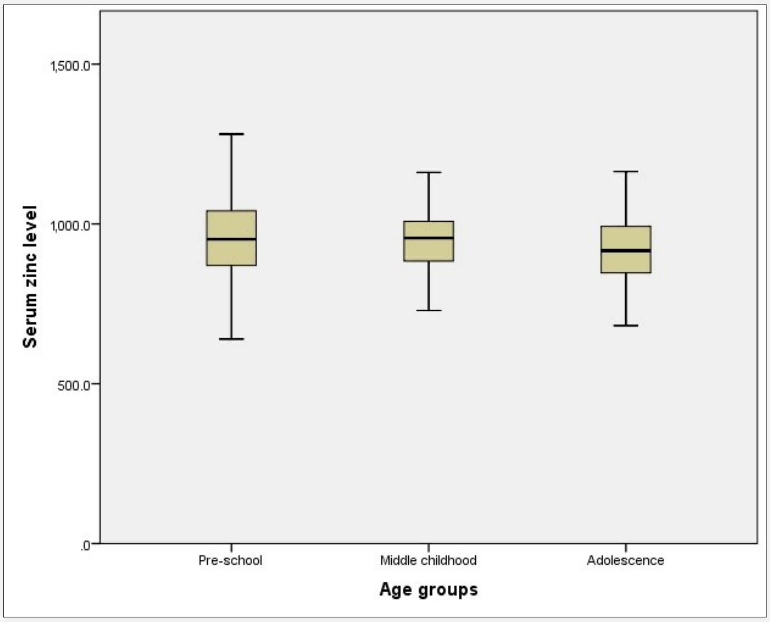

Figure 3. Serum zinc levels according to age.

RESULTS

Metabolic properties of groups formed according to vitamin D levels

In this study, out of a total of 541 cases, 213 (39.37%) were girls and 328 (60.63%) boys. The cases were divided into 3 groups according to their serum 25(OH)D levels. Eighty cases (14.79%) had deficiency and 99 cases (18.30%) had insufficiency while vitamin D levels were sufficiency in 362 (66.91%) of the cases. The difference between the groups was investigated by ANOVA (Table 1). Serum glucose levels did not change significantly according to the groups ($p = 0.137$). Zn levels were statistically significantly lower in the group with vitamin D deficiency ($p < 0.001$) (Figure 1). Age and BMI were significantly higher ($p < 0.001$). A statistically significant difference was found between the 3 groups in other parameters ($p < 0.001$). In order to investigate the significant difference between the groups, intragroup comparisons were made. In the group with 25(OH)D deficiency, BMI was statistically increased ($p < 0.001$), while the 25(OH)D level was significantly decreased ($p < 0.001$). Age, BMI, and triglycerides significantly increased ($p < 0.001$ for each), vitamin D, zinc, urea, creatinine, cholesterol ($p < 0.001$ for each), and HDL ($p = 0.013$) significantly decreased in the 25(OH)D level deficiency group compared to the sufficiency group. When the 25(OH)D level sufficiency and insufficiency groups were compared, BMI and triglycerides significantly increased ($p = 0.006$, $p = 0.014$ respectively), while 25(OH)D, zinc, urea, cholesterol, and HDL were significantly decreased ($p < 0.001$, $p < 0.001$, $p = 0.015$, $p = 0.002$, and $p < 0.001$ respectively) in the insufficiency group. There was no statistically significant difference in terms of gender between the groups separated according to vitamin D level ($p = 0.346$).

Metabolic properties of groups formed according to age

The cases were divided into 3 groups according to age and examined. Routine biochemistry parameters, 25(OH)D, and Zn levels were compared (Table 2). Vitamin D levels were found to be statistically significantly higher in preschool group ($p < 0.001$) (Figure 2). Serum Zn levels also showed significant variation between the groups ($p = 0.025$) (Figure 3).

In-group comparisons were made to investigate the significant difference between the separated groups according to age. In the preschool group, 25(OH)D levels were found to be statistically significantly higher ($p = 0.002$), while age, creatinine, and HDL levels were significantly lower ($p < 0.001$ for all) than in the middle childhood group. 25(OH)D, urea levels were significantly higher and age, BMI, creatinine, and triglycerides levels were significantly lower ($p < 0.001$ for all) in the preschool group compared to the adolescence group. In the middle group, compared to the adolescence group, 25(OH)D, zinc, urea, and HDL levels were significantly increased ($p < 0.001$, $p = 0.007$, $p < 0.001$, $p < 0.001$, respectively), age, BMI, creatinine, and triglycerides levels were statistically significantly decreased ($p < 0.001$ for all). When the preschool group and middle childhood were compared, no statistically significant difference was found between the two groups in terms of gender ($p = 0.193$). However, there was a significant difference in gender between middle childhood and adolescence groups and between preschool and adolescence groups ($p = 0.003$ and $p = 0.038$, respectively).

We found that 25(OH)D was negatively correlated with age ($r = -0.261$; $p < 0.001$) and BMI ($r = -0.308$; $p < 0.001$). We found a positive correlation between serum 25(OH)D and Zn levels ($r = 0.468$, $p < 0.001$).

DISCUSSION

Vitamin D insufficiency is an important global public health problem for developed countries as well as developing countries with a high prevalence [1]. Along with vitamin D deficiency, zinc deficiency also remains one of the most common public health problems related to micronutrient deficiency in some parts of the world. The determination of vitamin D and Zn status is important for intellectual achievements and academic performance, as well as for the growth development and health of school-age children. It is extremely beneficial and necessary to establish the levels of vitamin D and Zn and the relationship between them for the prevention of their deficiency, reducing the rate of growth and development retardation, regulating bone development and the developing immune system [13].

Many studies point to children with poor vitamin D levels, including in tropical countries. It is stated that lifestyle changes, limited time spent outdoors, insufficient exposure to sunlight, air pollution, skin pigmentation, and insufficient intake of vitamin D by diet are effective in the formation of this condition [14,15]. The prevalence of vitamin D deficiency, which is reported worldwide in children and adults, is about 30 - 80%, although it varies widely by country [4]. In our study, we found that vitamin D deficiency, which is a global public health problem, is high in children and adolescents, similar to other studies, and that vitamin D levels are the lowest in adolescents [8]. In a study that included 440 children and adolescents aged 0 - 16 years, it was shown that 25% of the cases had vitamin D deficiency and 15% had vitamin D insufficiency, and vitamin D deficiency increased with age [4].

Consistent with other studies, our study revealed that preschool children have the highest levels of vitamin D, and vitamin D deficiency is less common in this age group [4,16]. In a study by Mansbach et al. in the USA, it was shown that vitamin D insufficiency is lower under the age of 5 compared to the older age group [17]. The free administration of vitamin D to all babies since 2005 and for pregnant women and mothers during lactation since 2011 has largely prevented vitamin D deficiency in infants and children in Turkey [18].

Micronutrient deficiencies are frequently observed in overweight individuals as well as undernourished people [19,20]. In our study, we found a negative correlation between vitamin D levels and BMI. In previous studies, it has been found that vitamin D deficiency is more common in obese people [15,21]. Although the etiopathogenesis of vitamin D deficiency in obesity is not fully known, storage of vitamin D in a larger body fat pool may be effective due to the retention of vitamin D in subcutaneous adipose tissue in obese individuals. It has been stated that less physical activity outdoors and, consequently, reduced sunlight exposure, as well as decreased bioavailability and inadequate dietary intake, lead to a decrease in vitamin D production [22]. In addition, it has also been shown that vitamin D deficiency leads to an increase in adipose tissue as a result of differentiation in fat cells by increasing the number of vitamin D receptors in adipose tissue [21]. A prospective study showed that a decrease in the level of 25(OH)D increases the risk of myocardial infarction [23]. Adolescent obesity is associated with increased mortality in middle age [24]. However, the long-term effects of adolescent obesity on cause-specific mortality have not been well established. Vitamin D monitoring and replacement is important in adolescents in terms of preventing deaths from cardiovascular disease, cerebrovascular disease, and cancer since an increased BMI is associated with low vitamin D levels [20].

In some studies, vitamin D deficiency has been found to be more common in girls than in boys, and it has been stated that it varies according to socio-economic status and season [17,24]. In our study, vitamin D deficiency in girls was not statistically significant compared to boys. In a study examining 25(OH)D levels of 392 individuals in Lebanon, no significant difference was found according to gender [25]. Oren and his colleagues also found no significant differences in vitamin D levels according to gender in their studies and stated that the differences in vitamin D levels according to gender decreased [16]. In this case, clothing habits, spending more time outdoors and increased physical activity may be effective.

Zinc supplementation has positive effects on motor activity in infants, school success, and neuropsychological performance in school-age children. In one study, it was stated that in comparison with healthy controls, the ADHD child group had increased pro-inflammatory markers and lower serum zinc levels, which may contribute to hyperactivity [26]. Zn deficiency causes growth retardation in children. Although the disruption in linear growth is not directly specific to Zn deficiency, it is known to be a feature of Zn deficiency [27]. Despite its importance, the World Health Organization stated that 450,000 children under the age of 5 die annually due to zinc deficiency. It has been reported that the concentration of zinc in girls and boys in childhood is low and reaches its peak in adolescence, possibly due to increased physical activity [13]. When we examined the levels of Zn in preschool, school-age, and adolescents, we found that the lowest levels of Zn were in adolescence. Consistent with other studies, we did not detect any significant differences in serum Zn levels in terms of gender [13,28]. Liu et al. also found that in their study of 3,407 children, there was no difference in Zn levels according to gender [13]. Zinc deficiency can be caused mainly by various factors such as nutritional deficiencies and habits, parasitic infections, and environmental pollution. Only a small percentage of dietary zinc is absorbed, as is iron. It is known that some nutrients, vitamins, and minerals also interact with zinc, affecting its bioavailability. While reducing phytates, fibrous foods, inorganic iron, calcium, phosphates, copper, oxalate, cadmium, and soil zinc absorption, vitamin D, vitamin B6, proteins, methionine, wine, and D-penicillamine lead to increased absorption of Zn [29]. In addition, acute trauma, stress, and infection may cause an increase in hormones and cytokines that cause a lower plasma zinc concentration as a result of the sequestration of zinc in the liver and spleen [3].

Zn and vitamin D are important because they affect many functions. Intracellular zinc concentrations affect the activity of vitamin D-dependent genes, helping vitamin D to work actively. Vitamin D also has effects on Zn. In addition to its traditional role in Ca metabolism, vitamin D is also associated with better absorption of inorganic elements such as iron, zinc, copper, selenium [30]. In our study, we found a positive correlation between 25(OH)D and zinc levels. Shams et al. reported that there was a significant positive correlation between vitamin D and Zn concentrations in their study in which they examined 330 children with and without D hypovitaminosis [8]. This relationship can be explained by vitamin D and Zn malnutrition habits. Becker and Hoekstra found that when vitamin D was added to the diet of rats with vitamin D deficiency, Zn levels in the skeletal and soft tissues increased significantly at the 60th hour. They stated that as a result of treatment with vitamin D, the absorption of zinc and uptake in the bones increased [31]. It has been suggested that the increase in absorption may be the result of an increased need for zinc secondary to skeletal growth, and not from the direct action of the vitamin. Specifically, zinc facilitates bone formation by stimulating osteoblasts [32]. In a study in which serum-urine zinc, copper, and magnesium levels were measured in pediatric patients with vitamin D-resistant rickets, serum Zn levels were found to be high after high-dose vitamin D treatment [33]. These findings show that vitamin D has an effect on Zn absorption and metabolism as well as the primary effect on skeletal development.

In our study, high rates of vitamin D deficiency and insufficiency were detected in our group consisting of children and adolescents. Increased BMI and advanced age were found to be risk factors for vitamin D deficiency and insufficiency. At the same time, a correlation was found between vitamin D and zinc levels.

There were some limitations in our research. The design of our study was single-centered and cross-sectional. We believe that a larger, multicenter study will yield more accurate results on the actual prevalence. To our knowledge, many studies have examined vitamin D and zinc levels separately. They indicated the association of serum 25(OH)D concentrations with serum levels of other elements. However, the relationship between vitamin D and zinc has been investigated in only one study with a smaller number of cases. Our study is the first comprehensive study in the literature to evaluate vitamin D and zinc levels in children and adolescents and their relationships with each other.

Parents and teachers should be informed about proper dietary choices, appropriate and adequate exposure to the sun at school and at home, and physical activity. There is also a need for strategic actions to detect, prevent, and treat vitamin D and zinc deficiency in childhood and adolescence in public health and primary health care services in order to improve the status of vitamin D and thus zinc levels. According to the results of our study, vitamin D supplementation should be provided not only to infants and previously identified risk groups but also to children of all ages, including adolescents. Thus, the zinc level in our children will also increase and the rate of growth retardation will be reduced. With regular bone development and stronger immunity, they will be protected from diseases that cause serious morbidity and mortality.

Declaration of Interest:
The authors stated that there are no conflicts of interest regarding the publication of this article.

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