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Serum Vitamin D Levels in Children and Adolescents with Vasovagal Syncope, Syncope Due to Orthostatic Hypotension, and Cardiac Syncope

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What is already known on this topic?

- *Nowadays, a large number of studies indicate links between serum vitamin D level and impacts of dysfunction of the autonomic nervous system on cardiovascular system. The last one has also been shown to participate in the pathogenesis of syncope. To the best of our knowledge, there has been no research on a potential relationship between vitamin D levels and syncope due to orthostatic hypotension, as well as cardiac syncope in pediatric population.*

What this study adds to this topic?

- *The results of our research showed that children and adolescents with vasovagal syncope, syncope due to orthostatic hypotension, and cardiac syncope had a higher frequency of vitamin D deficiency than healthy pediatric individuals. These findings can be valuable in the development of effective management strategies for syncope in pediatric patients. Thus, we suggest that 25(OH)D should be analyzed in all children and adolescents with history of syncope.*

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ABSTRACT

Objective: The study aimed to compare vitamin D levels between children and adolescents with vasovagal syncope, syncope due to orthostatic hypotension, cardiac syncope, and healthy individuals and to investigate the correlations of 25(OH)D with main clinical parameters of syncope.

Materials and Methods: This study involved 83 children aged 8–17 years with syncope: 40 with vasovagal syncope, 24 with syncope due to orthostatic hypotension, and 19 with cardiac syncope. There were 24 healthy volunteers in the control group. Data concerning active standing test, electrocardiography, echocardiography, electroencephalography, and 24-hour Holter monitoring findings were collected. Serum vitamin D was evaluated by an enzyme-linked immunoassay technique test.

Results: The mean levels of serum 25(OH)D were decreased in children with vasovagal syncope (18.8 ± 5.9 ng/mL), syncope due to orthostatic hypotension (19.9 ± 6.7 ng/mL), and cardiac syncope (20.6 ± 7.3 ng/mL) in comparing with the control group (30.9 ± 5.9 ng/mL; $P < .001$). In patients with syncope due to orthostatic hypotension, vitamin D deficiency was associated with a reduction in systolic blood pressure ($r = 0.43$) and diastolic blood pressure ($r = 0.38$) within the first minute, lower systolic blood pressure ($r = 0.44$) within the third minute of active orthostasis ($P < .05$). There were significant correlations of vitamin D deficiency with parameters of cardiac autonomic activity pNN50 ($r = 0.49$), total power ($r = 0.39$), and low frequency index ($r = 0.35$) in children with cardiac syncope ($P < .05$), while heart rate variability was not affected in patients with vasovagal syncope and syncope due to orthostatic hypotension ($P > .05$).

Conclusion: Children and adolescents with vasovagal syncope, syncope due to orthostatic hypotension, as well as cardiac syncope had higher frequency of vitamin D deficiency than healthy pediatric controls. This provides a new approach to syncope management in pediatric population, requiring further studies.

Keywords: Vasovagal syncope, syncope due to orthostatic hypotension, cardiac syncope, cardiac autonomic dysfunction, vitamin D deficiency, children and adolescents

INTRODUCTION

Syncope is defined as an abrupt transient loss of consciousness which is characterized by secondary inability to maintain postural tone, followed by spontaneous complete recovery. It is considered to be one of the most common pediatric illnesses that lead to increased number of ambulatory visits and require further assessment by a pediatrician and pediatric

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cardiologist.[1] One study has shown that up to 15% of children had experience of at least 1 episode of syncope to the end of childhood.[2] Of undifferentiated pediatric patients with symptoms of syncope in the emergency department, the majority presented with the symptoms of vasovagal syncope (VVS) and syncope due to orthostatic hypotension (OH), approximately 9% of children presented with the symptoms of neurological disorders, and only 2% presented with the symptoms of cardiac syncope (CS).[3,4] Traditionally, syncope is differentiated into 3 distinct types—VVS, syncope due to OH, and CS.[5] The underlying pathophysiology of syncope in all cases is due to a transient decrease in cerebral blood flow secondary to decreased blood pressure. This in turn is due to cardiac output and peripheral vascular resistance.[6]

Several reports have indicated that orthostatic intolerance including VVS and postural tachycardia syndrome (POTS) in children is associated with vitamin B1 deficiency,[7] vitamin B6 deficiency,[8] vitamin B12 deficiency,[9,10] and hyperhomocysteinemia.[8,11] Recent research found interaction between low vitamin D status and nonskeletal chronic conditions, particularly cardiovascular diseases.[12] There have also been a large number of reports analyzing the association of serum vitamin D and cardiac autonomic dysfunction,[13-15] but studies including the assessment of vitamin D in pediatric patients with different types of syncope, not only VVS, are quite limited.

The aim of the research was to study serum vitamin D concentrations and vitamin D status in children and adolescents with different syncope types (VVS, syncope due to OH, CS) and the healthy ones, as well as to determine correlations between serum vitamin D measurements and main clinical parameters of syncope. It was suggested that results of this study will help to better understand the role of vitamin D deficiency in the pathogenesis of pediatric VVS, syncope due to OH, and CS.

MATERIALS AND METHODS

Study Population and Data Collection

This study involved 83 children aged 8-17 years referred to the pediatric hospital in Ternopil (Ukraine) due to syncope symptoms during the 2018-2020 period. Data concerning history taking and physical examination including active standing test,[16] electrocardiography (ECG) in 12 leads, echocardiography, and electroencephalography findings were collected. Diagnostic criteria of European Society of Cardiology (2018) were used to diagnose various types of syncope.[5] As a result of the survey, VVS was diagnosed in 40 children and adolescents, syncope due to OH in 24 pediatric patients, and CS in 19 children and adolescents. There were also 24 healthy volunteers in the control group.

Inclusion Criteria

All children and adolescents involved in the study satisfy the following criteria.

Inclusion criteria for VVS were: (1) syncope triggered by feeling of dread, pain, or prolonged standing position and preceded by typical gradual prodromal period (paleness, excessive perspiration, and/or nausea); (2) at least 1 syncopal episode in the last month; (3) normal physiological responses during an active standing test; (4) structurally normal hearts, and normal heart rhythm; (5) electroencephalography showed normal results; and (6) there was no other evident etiology for syncope.

Inclusion criteria for group of syncope due to OH: (1) syncope episodes happened when standing or after standing, and/or prolonged standing; (2) during the third minute of active standing test, child experienced a drop in systolic blood pressure (SBP) from baseline of ≥20 mmHg or diastolic blood pressure (DBP) of ≥10 mmHg, or a reduction in SBP to <90 mmHg that triggered spontaneous symptoms; (3) at least 1 episode of syncope in the last month; (4) absence of structural heart diseases and arrhythmia; (5) electroencephalography showed normal results; and (6) child did not have evidence of other etiology for syncope.

Inclusion criteria for CS were: (1) exercise-induced syncope or in a supine position, (2) pathological changes on the ECG (bifascicular block; other disorders of intraventricular conduction with the duration of QRS greater than 0.12 seconds; second-degree sino-atrial block, type 2; second- or third-degree atrioventricular block; stable sinus bradycardia or atrial fibrillation with the heart rate (HR) <50 beats/min; Brugada syndrome; paroxysmal ventricular or supraventricular tachycardia; pre-excitation syndromes; long or short QT syndrome; right ventricular arrhythmogenic cardiomyopathy with the epsilon waves and negative T wave in the right precordial leads; early repolarization syndrome; hypertrophic cardiomyopathy with the left ventricular hypertrophy), and/or pathological changes on the echocardiogram (structural heart disease); (3) at least 1 syncopal episode during the last month; (4) normal physiological response in active standing test; (5) normal electroencephalography results; and (6) absence of other conditions known to cause syncope.

Inclusion criteria for control group: (1) negative history of syncope, (2) unremarkable results of a clinical examination, routine blood and urine analyses, and (3) normal physiological responses during an active standing test.

Exclusion Criteria

Patients of all groups will be excluded based on the following exclusion criteria: (1) parents and children refuse consent to participate in the study; (2) vitamin D and/or calcium supplements taken within the last year; (3) any other acute or chronic diseases including malabsorption disorders, overweight or obesity, chronic renal disease or renal transplant, hypertension, hereditary disorders cause impaired metabolism of vitamin D; and (4) seasonal period between May and August.

MATERIALS AND METHODS

Serum Vitamin D Measurement and Assessment Method

Blood samples were collected from the study participants in the period from September to April in order to exclude the influence of seasonal increment of sun exposure to obtain results. All of the samples were frozen and then stored at −80°C until further analysis. A quantitative sandwich ELISA (Monobind Inc., USA) was performed according to the manufacturer's instructions in the Scientific and clinical laboratory of Ivan Horbachevsky Ternopil National Medical University (Ternopil, Ukraine) for the measurement of 25(OH)D in serum. Recent clinical guidelines[17] describe serum 25(OH)D concentration below 20 ng/mL as

vitamin D deficiency, while values between 20 and 30 ng/mL are suboptimal and 30-50 ng/mL are optimal vitamin D level.

24-Hour Holter Monitoring

Heart rhythm recordings were conducted over a 24-hour period using a 3-channel Holter monitor (SDM3, Ukraine) in all groups of participants. Heart rate variability (HRV) parameters were analyzed using software package. After artifact correction, the time- and frequency-domain measurements were calculated. The standard deviation of the averages of R-R intervals in 5-min segments, root mean square of successive RR interval differences (RMSSD), and the percentage of consecutive R-R intervals that differ by more than 50 ms (pNN50) were used as time–domain indices. The frequency–domain analysis of HRV consisted of the total power (TP), very low-frequency bands (VLF), low-frequency index (LF), high-frequency index (HF), and LF/HF ratio.[18]

Statistical Analysis

All statistics were analyzed using the Statistical Package for Social Sciences 12.0 Statistical Package Program for Windows. Smirnov–Kolmogorov test was used to test the normality of the data distribution. Continuous variables for data following normal distribution were reported as mean ± standard deviation (SD), and continuous variables for data not following normal distribution were expressed as the median (M) with interquartile range (IQR). Categorical data were expressed as a number (n) and percentage (%). One-way analysis of variance (ANOVA) was used in order to compare continuous variables for more than 2 groups. Intra-group differences were evaluated using Tukey's post hoc analysis. Differences in categorical variables between groups were examined by Pearson's chi-square (χ^2) test. Relationships between serum vitamin D level and main clinical parameters in syncope groups were examined using Spearman linear correlation analysis. Two-tailed *P* values less than .05 were considered to be statistically significant.

Ethics Statement

Ethical approval for this clinical study was obtained from the Ivan Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine, Approval No: 4, Date: 18.04.2018. All participants signed written informed consent before the study.

RESULTS

Serum Vitamin D Concentrations

There was no significant clinical difference between the VVS group, syncope due to OH group, CS group, and control group in terms of participants' age, gender, body mass index (BMI), baseline SBP, DBP, and HR, as described in Table 1. Age at first syncopal event, number of syncopal episodes, duration of the last pre-syncope, syncope, and post-syncope symptoms did not differ significantly between subjects with syncope ($P > .05$). It helped to exclude the influence of these factors on the serum vitamin D concentration in patients who had syncope. Serum vitamin D levels in patients with different syncope types and healthy children are presented in Table 1 and Figure 1. Post hoc analysis has shown that 25(OH)D concentrations in children with VVS, syncope due to OH, and CS were lower than the values of the control group ($P < .001$). However, no significant difference was observed between the 3 syncope groups in this regard ($P > .05$).

Vitamin D Status

The next step of the research was to evaluate vitamin D status in examined patients (Table 2). Children and adolescents with syncope had significantly higher frequency of vitamin D deficiency than healthy controls. At the same time, subjects with syncope reported having lower rate of the optimal vitamin D levels which differed significantly compared to healthy individuals. Nevertheless, we did not evaluate the differences in the prevalence of suboptimal levels of vitamin D between research groups. Statistically significant difference for optimal vitamin

Table 1. Demographic, Clinical, and Biochemical Variables of Patients

Variables	VVS Group (n = 40)	Syncope Due to OH Group (n = 24)	CS Group (n = 19)	Control Group (n = 24)
Age, years	14.5 ± 2.2	14.8 ± 2.2	13.7 ± 2.8	13.7 ± 2.4
Males/females, n (%)	20 (50.0)/20 (50.0)	16 (66.7)/8 (33.3)	11 (57.9)/8 (42.1)	16 (66.7)/8 (33.3)
BMI, kg/m^2	20.1 ± 3.5	19.4 ± 2.6	20.7 ± 5.9	18.8 ± 2.6
Age of the first syncopal event, years	13.2 ± 2.7	12.7 ± 3.9	11.8 ± 2.8	-
Number of syncopal events, M (IQR), n	2.0 (1.0, 4.1)	4.0 (2.0, 11.0)	2.5 (1.0, 5.0)	-
Duration of the last pre-syncope symptoms, M (IQR), minute	0.5 (0.3, 1.0)	0.5 (0.17, 1.0)	0.3 (0.2, 0.8)	-
Duration of the last syncope symptoms, M (IQR), minute	1.0 (0.5, 2.0)	1.0 (0.5, 2.0)	1.0 (0.3, 2.0)	-
Duration of the last post-syncope symptoms, M (IQR), minute	45.0 (15.0, 60.0)	30.0 (10.0, 60.0)	60.0 (15.0, 140.0)	-
Baseline SBP, mmHg	107.5 ± 11.5	104.2 ± 11.1	106.6 ± 10.8	106.7 ± 5.5
Baseline DBP, mmHg	67.3 ± 9.0	64.6 ± 7.2	66.1 ± 7.4	65.8 ± 6.5
Baseline HR, bpm	71.4 ± 7.1	69.1 ± 8.1	68.3 ± 11.3	72.5 ± 6.0
25(OH)D level, ng/mL*	18.8 ± 5.9	19.9 ± 6.7	20.6 ± 7.3	30.9 ± 5.9

*ANOVA, $P < .000001$.
BMI, body mass index; CS, cardiac syncope; DBP, diastolic blood pressure; HR, heart rate; IQR, interquartile range; M, median; OH, orthostatic hypotension; SBP, systolic blood pressure; VVS, vasovagal syncope; 25(OH)D, 25-hydroxyvitamin D.

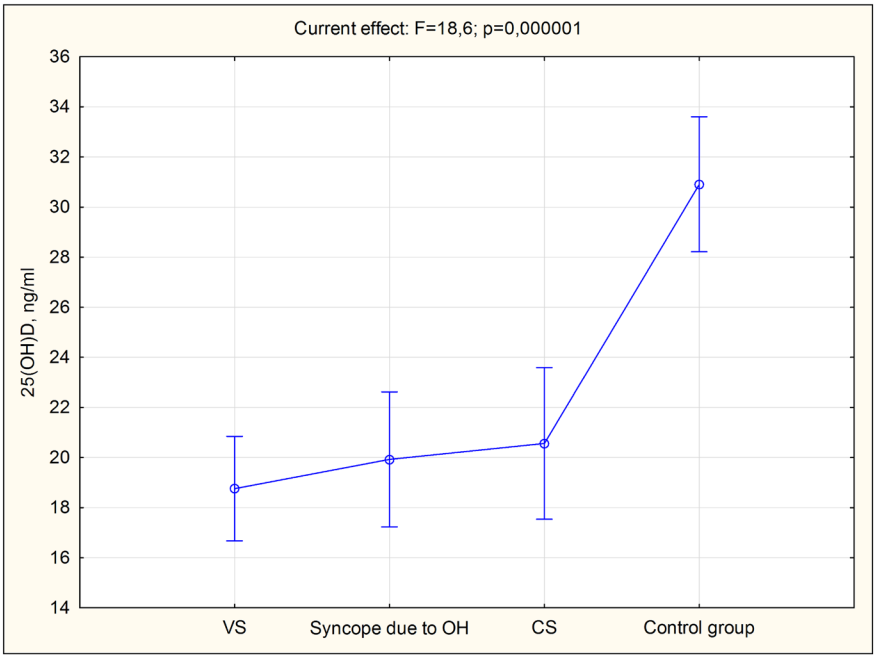

Figure 1. Mean ± SD serum 25(OH)D level in children of different groups. 25(OH)D, 25-hydroxyvitamin D; VVS, vasovagal syncope; OH, orthostatic hypotension; CS, cardiac syncope.

D effects and vitamin D deficiency prevalence in all syncope groups was confirmed with post hoc analysis ($P < .01$).

Associations of Vitamin D Level in Serum with Main Clinical Parameters of Syncope

As shown in Table 3, significant correlation was observed between serum levels of vitamin D and duration of the last syncopal episode, circadian index, and the number of supraventricular extrasystoles within 24-hour Holter monitoring in VVS group. There were also relationships between serum 25(OH)D concentration and duration of the last pre-syncope symptoms, baseline SBP, SBP, and DBP in the first minute of active standing test and SBP in the third minute of active standing test in the patient group with syncope due to OH. By contrast, serum vitamin D was correlated with the number of syncopal events, and duration of all arrhythmia episodes measured during Holter monitorization in children and adolescents with CS. We additionally investigated positive correlations between 25(OH)D concentration and HRV parameters pNN50, TP, and LF in children and adolescents with CS. There were no relationships between serum vitamin D and age, sex, and BMI in the patients of all groups with syncope.

Table 2. Vitamin D Status in Examined Patients

Vitamin D Status, n (%)	VVS Group (n = 40)	Syncope Due to OH (n = 24)	CS (n = 19)	Control Group (n = 24)
Optimal vitamin D effects*	3 (7.5)	2 (8.3)	2 (10.5)	13 (54.2)
Suboptimal status	13 (32.5)	9 (37.5)	8 (42.1)	1 (45.8)
Vitamin D deficiency*	24 (60.0)	13 (54.2)	9 (47.4)	0 (0.00)

*Post hoc test results, $P < .01$.
CS, cardiac syncope; OH, orthostatic hypotension; VVS, vasovagal syncope.

DISCUSSION

In the current study, serum 25(OH)D level was lower in all syncope groups of children and adolescents than that in healthy individuals. Moreover, there was no statistically significant difference between patients with VVS, syncope due to OH and CS in the serum vitamin D concentration. Some recent studies have shown that VVS in children is associated with reasonably low vitamin D levels.[14,19] Gialini et al[20] reported an association between probability of OH and circulating vitamin D levels in elderly males. Despite this fact, Laird et al[21] published another study results in which the authors described that vitamin D concentration was not significantly associated with OH in older adults. There are no comparable researches about vitamin D level assessment in pediatric patients with syncope due to OH.

While the exact pathogenic mechanisms of VVS, POTS, and OH remain uncertain, these disorders are established to have similar etiologies.[22,23] Dysfunction of autonomic nervous system has been shown to be involved in the development of VVS, POTS, and OH in children and adolescents.[23-25] Vitamin D acts as a neuroactive compound which plays a crucial role in maintaining the balance of autonomic nervous system. Autonomic dysfunction alters the gene expression which has participated in calcium metabolism before and after differentiation of the neural cells that gives rise to neurons of the parasympathetic and sympathetic nervous system.[15] In addition, vitamin D induces brain cell proliferation and differentiation, promotes calcium signaling in the brain, and has neurotrophic and neuroprotective effects that may also modify neurotransmission and synaptic plasticity.[26] Vitamin D also modulates hypothalamic–pituitary–adrenal axis, which participates in the production of monoamine neurotransmitters such as dopamine, epinephrine, and norepinephrine.[27,28] There is reasonable evidence implicating neurohormones

Table 3. Correlation Matrix of Serum Vitamin D Levels and Main Clinical Parameters in Syncope Groups

Parameter	Vitamin D Levels		
	VVS Group (n = 40)	Syncope Due to OH Group (n = 24)	CS Group (n = 19)
Age, years	0.1237	−0.2441	−0.1022
Sex	0.0325	−0.0128	0.0208
BMI, kg/m^2	−0.0552	−0.0244	−0.1684
Number of syncopal events, n	0.0574	−0.2520	**−0.4818**
Duration of the last pre-syncope symptoms, minute	0.1366	**0.3850**	−0.1950
Duration of the last syncope symptoms, minute	**0.2811**	0.2349	−0.0396
Duration of the last post-syncope symptoms, minute	−0.1920	0.0469	−0.0505
Supine HR, bpm	0.1337	0.2085	0.1469
Supine SBP, mmHg	0.0851	**0.4198**	0.1730
Supine DBP, mmHg	0.0104	0.2830	−0.2485
SBP on the first minute of active standing test, mmHg	0.0784	**0.4284**	−0.0251
DBP on the first minute of active standing test, mmHg	0.0484	**0.3811**	−0.0534
SBP on the third minute of active standing test, mmHg	0.0352	**0.4401**	0.0110
DBP on the third minute of active standing test, mmHg	0.0432	0.2345	−0.1365
Circadian index, units	**−0.2741**	−0.1961	0.0981
Duration of all tachycardia episodes within 24-hour Holter monitoring, %	−0.0532	−0.0843	−0.2239
Duration of all bradycardia episodes within 24-hour Holter monitoring, %	−0.0185	−0.1437	0.2348
Duration of all arrhythmia episodes within 24-hour Holter monitoring, %	−0.0349	−0.0808	**0.3809**
Amount of ventricular extrasystoles within 24-hour Holter monitoring, %		-	−0.0283
Amount of supraventricular extrasystoles within 24-hour Holter monitoring, %	**−0.2705**	-	0.0716
SDANN, ms	−0.0775	0.2253	−0.1785
RMSSD, ms	−0.0581	0.0321	−0.0361
pNN50, %	−0.0721	−0.1799	**0.4894**
TP, ms^2	0.1203	0.1395	**0.3891**
VLF, ms^2	0.1039	0.2185	0.2879
LF, ms^2	0.1075	−0.0452	**0.3521**
HF, ms^2	0.1452	−0.0446	0.3416
LF/HF ratio	−0.0859	0.1199	−0.2322

Bold values indicate statistically significant results in comparing with the control group.
BMI, body mass index; CS, cardiac syncope; DBP, diastolic blood pressure; HF, the high frequency index; HR, heart rate; LF, the low frequency index; OH, orthostatic hypotension; pNN50, the proportion of adjacent normal R-R intervals <50 ms; RMSSD, the root of the 24-hours square; SBP, systolic blood pressure; SDANN, standard deviations of the averages of the R-R intervals in all 5-min segments of R-R intervals; TP, the total power; VLF, the very low frequency band; VVS, vasovagal syncope.

such as epinephrine, norepinephrine, and arginine vasopressin changes in certain aspects of VVS development.[29]

It was reported that the mid-brain and brainstem in which a number of the neurons for the autonomic nervous system are located have been shown to have a high number of vitamin D receptors, thus suggesting the hypothesis that vitamin D probably is involved in the modulation of the control centers of autonomic nervous system.[30,31] Moreover, Dogdus et al[32] found that significant correlation between vitamin D deficiency and impaired cardiac autonomic functions measured by heart rate variability parameters and showed that cardiac autonomic dysfunction was improved after vitamin D supplementation in healthy adults. These findings suggest that vitamin D can be directly linked to the function of the cardiac autonomic nervous system and as a result, to the subsequent risk of cardiovascular disorders.[33]

This study indicates that vitamin D deficiency was common among children and adolescents with syncope and demonstrates a prevalence of 60.0% in the VVS group, 54.2% in the group of syncope due to OH, and 47.4% in the group of CS which are not statistically different. These results are partially comparable with other studies of 25(OH)D levels in children with VVS which showed that 33.8% had vitamin D deficiency[19] and 60.0%[14] and suggested that 25(OH)D may be involved in the pathological mechanism of different syncope types by affecting cardiac autonomic function.

This study explored certain relationship between clinical characteristics of syncope and serum vitamin D concentration. Levels of vitamin D have been associated with duration of symptoms preceding a syncopal episode in patients with syncope due to OH and with duration of last syncopal symptoms in individuals with VVS. Furthermore, decreased levels of serum vitamin D in children and adolescents with CS were accompanied by more frequent syncope events. These correlations are further evidence of possible role of vitamin D deficiency in the development of pediatric syncope.

It was found that the supine systolic blood pressure was lower in vitamin deficiency patients with syncope due to OH. Moreover, OH in patients with decreased serum vitamin D concentration was associated with lower SBP and DBP at first

minute of active standing test and lower SBP at third minute of active orthostasis. Recent studies show that 25(OH)D may contribute to OH.[20,21,34] Vitamin D receptors were found in vascular smooth muscle and endothelial and cardiac cells. These results indicate that vitamin D can induce changes in vasomotor and cardiac response in orthostasis.[35] Several reports indicated that vitamin D supplementation may decrease the probability of transient loss of consciousness in adults via improvement of muscle strength and balance.[36,37] These findings may lead to clarification of syncope pathophysiology in children and adolescents with OH and require further study.

Zhang et al[14] determined a positive correlation between vitamin D levels and rMSDD values, suggesting that pediatric patients with VVS may have decreased parasympathetic nervous tone as a result of vitamin D deficiency. Zou et al[19] reported that rMSDD parameter was decreased in children with VVS and vitamin D deficiency compared to children with sufficient 25(OH)D status. Although our results showed that HRV parameters did not correlate with serum 25(OH)D level in VVS group and syncope due to OH group, positive correlations between vitamin D concentration and pNN50, TP, and LF parameters of HRV in CS group of patients were detected. This suggests that low serum vitamin D levels are associated with cardiac autonomic dysfunction which indicated an increased sympathetic modulation and decreased vagal tone in children and adolescents with CS. Overactivity of sympathetic nervous system and parasympathetic impairment are well-known negative prognostic factors for morbidity and mortality associated with arrhythmia and sudden cardiac death.[38,39]

Study Limitations

The present study has several limitations, including a relatively small number of pediatric patients, which might have led to bias. Moreover, 25(OH)D levels might be affected by different exposure to the sun in autumn, winter, and spring seasons, suggesting influence on the results' accuracy. Although a head-up tilt test performance is not obligatory for the diagnosis of syncope, it would be a good idea to study the vitamin D status in tilt test-positive and tilt test-negative patients. The relationship between vitamin D level and salt with fluid intake among children and adolescents with syncope due to OH also was not reached in this study. In addition, we did not study the effectiveness of vitamin D supplements in pediatric patients with syncope. Further studies are needed to overcome these shortcomings.

CONCLUSION

The results of our research showed that children and adolescents with VVS, syncope due to OH, as well as CS had a higher prevalence of vitamin D deficiency when compared to healthy controls. Thus, we recommend the assessment of serum 25(OH)D profile of all children and adolescents with a history of syncope. Vitamin D deficiency was associated with lower SBP and DBP within the first minute of active standing test and lower SBP within the third minute of active orthostasis in patients with syncope due to OH. The correlations between the level of vitamin D and cardiac autonomic dysfunction parameters (pNN50, TP, and LF) in children and adolescents with CS were detected, while HRV parameters were not affected in patients with VVS and syncope due to OH. This provides a new approach to syncope management in pediatric population, requiring further studies.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ivan Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine (Approval No: 4, Date: 18.04.2018).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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