Article's History: Received: 29.03.2023; Revised: 19.05.2023; Accepted: 26.06.2023

Bulletin of Medical and Biological Research

Vol. 16, No. 2
2023

DOI: 10.61751/bmbr.2706-6290.2023.2.78

Journal homepage: https://bmbr.com.ua/en

UDC 616.12-008.316-06:616.8-009.832-053.2

Patophysiological basis of folate cycle disorders and vitamin D deficiency in the development of syncope in childhood

Tetiana Kovalchuk*

PhD in Medical Sciences, Associate Professor
I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine
46001, 1 Maidan Voli, Ternopil, Ukraine
https://orcid.org/0000-0003-2455-3278

Oksana Boyarchuk

Doctor of Medical Sciences, Professor
I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine
46001, 1 Maidan Voli, Ternopil, Ukraine
https://orcid.org/0000-0002-1234-0040

Abstract. There are many reports about the role of vitamins B6, B9, B12, and D in the development of cardiovascular diseases. However, most of them relate mainly to the adult population and are limited relative to grades in children with syncope. Understanding the role of these vitamins in the pathogenesis of syncope will help expand the range of therapeutic and preventive care for children. The purpose of the study was to analyse current scientific achievements regarding the role of the folate cycle and vitamin D in the genesis of syncope in childhood. The PubMed Medline and Scopus databases were used and the following search terms were used: "syncope" and "vitamin B"; "syncope" and "homocysteine"; "syncope" and "vitamin D". The paper summarises the role of vitamin B12 deficiency in delayed myelination and nerve conduction, increased serum norepinephrine levels, and possible pathogenetic mechanisms for the development of non-cardiogenic syncope. Scientific facts of the effect of vitamins B1, B6, and B9 on the functioning of the cardiovascular and nervous systems in children are described. The prevalence of vitamin D deficiency in 60-73% of children with vasovagal syncope and its relationship with the symptoms of the disease was established. Probable pathogenetic mechanisms of vitamin D deficiency in the development of syncope, namely a decrease in peripheral vascular resistance, a violation of neuronal conduction of the baroreflective mechanism, and heart muscle dysfunction, are analysed. The findings will allow doctors and researchers to better approach the diagnosis, prevention, and treatment of syncope in childhood and can serve as a basis for developing new strategies to manage the condition and improve medical practices

Keywords: vitamins; homocysteine; vasovagal syncope; syncope due to orthostatic hypotension; cardiogenic syncope; children

INTRODUCTION

Recent studies give every reason to believe that vitamins B6, B9, B12, and D affect the functioning of the cardiovascular and nervous systems, although the pathogenetic mechanisms of such effects are still poorly understood and unclear. The folate cycle enzymes methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR), and methionine synthase reductase (MTRR) are vital in the formation of cellular homeostasis due to their key functions in the single-carbon cycle, which includes the metabolism of methionine and folate, and the synthesis of protein, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA). The role of polymorphism of these genes in the development of diseases of the cardiovascular system (CVS) – metabolic syndrome, vascular atherosclerosis, arterial hypertension, myocardial infarction, stroke, thrombosis and thromboembolism – has been proven. In addition, there is no doubt that vitamin D deficiency is associated with various risk factors for CVS diseases associated with high-

Suggested Citation:
Kovalchuk T, Boyarchuk O. Patophysiological basis of folate cycle disorders and vitamin D deficiency in the development of syncope in childhood. Bull Med Biol Res. 2023;16(2):78–85. DOI: 10.61751/bmbr.2706-6290.2023.2.78

*Corresponding author

er mortality and the incidence of cardiovascular events. Considering the above facts, studies of folate cycle disorders and vitamin D deficiency are scientifically based and relevant from the standpoint of a better understanding of the pathogenetic mechanisms of transient loss of consciousness in children.

Vitamins B6 (pyridoxine), B9 (folic acid), and B12 (cyanocobalamin) are important cofactors in the folate and single-carbon cycles. Low levels of these vitamins are often consequences of hyperhomocysteinemia and independent risk factors for CVS, dementia, and depression [1-3]. Serum vitamins B6, B9, B12, and homocysteine levels depend on actual B vitamin intake and polymorphism of the MTHFR, MTR, and MTRR genes [4, 5]. A.D. Kaye *et al.* [6], A. Ueno *et al.* [7] proved the effectiveness of pyridoxine, folic acid, and cyanocobalamin preparations in reducing homocysteine levels in hyperhomocysteinemia. However, W. Herrmann *et al.* [8] were unable to demonstrate a reduction in the risk of CVS disease against the background of reduced homocysteine with vitamin supplements. Although the treatment of hyperhomocysteinemia with high doses of B vitamins does not have a positive effect on the secondary prevention of CVS diseases, the role of homocysteine in the primary prevention of diseases is poorly understood.

Vitamin D receptors have been shown to be found in most human cells and tissues, which indicates numerous non-intestinal effects of the vitamin, and highlights its special role in the functioning of the cardiovascular system. Vitamin D deficiency is associated with various risk factors for cardiovascular disease associated with increased mortality and the incidence of cardiovascular events in adults. Thus, A. Nitsa *et al.* [9] substantiated the role of vitamin D in the regulation of blood pressure by its effect on endothelial and smooth muscle cells of the vascular wall. N. Cosentino *et al.* [10] summarised several mechanisms that link vitamin D deficiency to cardiovascular risk factors, namely activation of the renin-angiotensin-aldosterone system, abnormal nitric oxide regulation, oxidative stress, and altered inflammatory pathways. However, the results of recent randomised controlled trials of J.E. Manson *et al.* [11, 12] do not confirm any benefit of vitamin D supplementation in the treatment of CVS diseases.

Considering all the above facts, the purpose of the study was to analyse current scientific achievements regarding the possible role of homocysteine and vitamins B6, B9, B12, and D in the pathogenetic mechanisms of syncopal states in children.

THE PROCESS OF SELECTING SCIENTIFIC PAPERS BY RESEARCH SUBJECT

The following search terms were used for the review: "syncope" and "vitamin B"; "syncope" and "homocysteine"; "syncope" and "vitamin D" in the PubMed Medline and Scopus databases. The full texts of papers in English published over the past 10 years were included in the study (January 2013 – December 2022). The results of the literature search are presented in Figure 1 as a flowchart Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13].

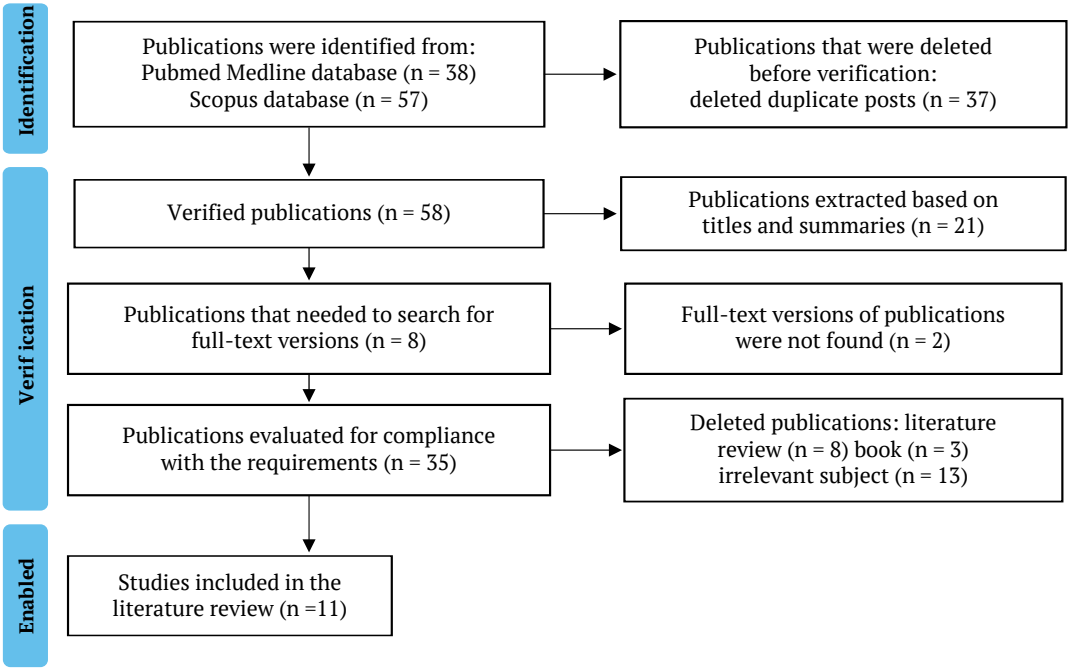

Figure 1. Prisma flowchart of the selection process for scientific publications on the research subject
Source: [13]

A total of 95 papers were identified – 38 in PubMed Medline and 57 in Scopus. Due to duplicates, 37 sources were excluded from the study. After the verification procedure of 58 publications, 47 of them were removed from the search based on irrelevant research subjects, the lack of full-text versions of study's and the results of their own experiments. Only 11 scientific sources were checked for compliance with the search subject and are reflected in Table 1. These publications have become key in the current understanding of the state of the problem of the role of homocysteine and vitamins B6, B9, B12, and D in the pathogenetic mechanisms of syncope formation in children.

Table 1. Studies that examined folate cycle and vitamin D scores in patients with syncope

Study	Country, year	Patient group, n	Diagnosis	The parameter that was defined	Characteristics of the indicator
A. Pektas *et al.* [14]	Turkey, 2018	children, 160	VS	vitamin B12	reduced
T. Öner *et al.* [15]	Turkey,2014	children,125	VS	vitamin B12 vitamin B9	reduced not changed
Y. J. Kong *et al.* [16]	China, 2022	children, 122	VS	vitamin D	deficit
Y. Xiao *et al.* [17]	China, 2022	children,142	VS SPOT OH	vitamin D	reduced
R. Zou *et al.* [18]	China, 2021	children, 130	VS	vitamin D	deficit
Q. Zhang *et al.* [19]	China, 2021	children, 76	VS	vitamin D	reduced
A. Gilani *et al.* [20]	United Kingdom, 2021	adults,7 735	OH	vitamin D	unchanged reduced deficit
S. Usalp *et al.* [21]	Cyprus, 2020	adults,75	VS	vitamin D vitamin B12	reduced reduced
R.R. Hesselbrock *et al.* [22]	USA, 202	adult, 1	syncope	vitamin B12	deficit
H.M. Serin *et al.* [23]	Turkey, 2019	children, 6	syncope	vitamin B12	deficit
Y. Li *et al.* [24]	China, 2018	children, 35	SPOT	homocysteine	increased

Notes: VS – vasovagal syncope, SPOT – Syndrome of Postural Orthostatic Tachycardia, OH – orthostatic hypotension
Source: developed by the authors based on the results of a literary search

INDICATORS OF THE FOLATE CYCLE IN CHILDREN AFTER SYNCOPE

The results of the search suggest that only two studies examined vitamin B12 levels in children with vasovagal syncope (VS). Thus, A. Pektas *et al.* [14] showed that serum vitamin B-12 concentrations in tilt-positive children were substantially lower than in tilt-negative children with VS. Overall, the prevalence of vitamin B12 deficiency was 100.0% in cardioinhibitory, 45.5% in vasodepressive, 91.7% in mixed VS types, and 92.3% in postural orthostatic tachycardia syndrome (SPOT). Furthermore, T. Öner *et al.* [15] examined plasma concentrations of vitamin B12 in patients with VS and healthy children and established the prevalence of their deficiency in 47.2% and 18.2% in the groups, respectively. In patients with SPOT, vitamin B12 deficiency was reported in 62.8%, and in children with syncope and without SPOT – in 47.2 %. As a result, both groups of authors suggested that cyanocobalamin may be involved in the pathogenetic mechanisms of syncope development.

Vitamin B12 has been shown to be a cofactor of at least three enzymes: (1) methylmalonyl-coenzyme A (CoA) mutase, which catalyses the isomerisation of methylmalonyl-CoA to succinyl-CoA during myelin synthesis; (2) phentolamine-N-methyltransferase, which is involved in the conversion of norepinephrine to epinephrine; and (3) catechol-O-methyltransferase, which is necessary for the breakdown of catecholamines [25, 26]. Thus, vitamin B12 deficiency is pathophysiologically characterised by delayed demyelination and nerve conduction, and increased serum norepinephrine levels [27]. As is known, it is the pathological Bezold-Jarisch reflex with a decrease in sympathetic impulses and an increase in vagal effects against the background of inadequate norepinephrine release that is one of the key mechanisms for the development of non-cardiogenic syncope [28, 29]. Therefore, it is logical to assume that vitamin B12 deficiency can affect the autonomic regulation of cardiac activity, just as it occurs with VS [15]. In addition, vitamin B12 deficiency is often diagnosed in patients with impaired autonomic control of CVS activity against the background of diabetes mellitus, atherosclerosis, and multiple sclerosis [30, 31].

Y. Liu *et al.* [32] have shown that both low and high levels of vitamin B12, and low serum folic acid levels, are associated with an increased risk of CVS mortality among people with diabetes mellitus. X. Xu *et al.* [33] established that dietary folic acid deficiency negatively correlates with all-cause mortality, cardiovascular disease mortality, and cancer mortality in men, and all-cause and cardiovascular disease mortality in women, and proved that increased dietary folic acid intake can reduce the risk of mortality in adults with diabetes in the United States. An analysis of 884 randomised controlled intervention studies among 883 627 participants found that folic acid supplementation reduced the risk of stroke [34]. In another UK cohort study involving 115 664 respondents, folic acid intake was found to be associated with a 5% reduction in the risk of cardiovascular events and a 10% reduction in the risk of mortality from cardiovascular diseases [35].

The beneficial effect of folic acid on the human body can be explained by several likely mechanisms. Firstly, folic acid is a cofactor of methionine synthase, which catalyses the conversion of homocysteine, so a decrease in vitamin B9 is always associated with hyperhomocysteinemia. Second, the polymorphism of 5.10-methylenetetrahydrofolate reductase, which is a critical component in folic acid metabolism due to its role in directing folic acid metabolites to the DNA methylation pathway and from the DNA synthesis pathway, can modulate subjects' susceptibility to numerous birth defects, cancer, cardiovascular, and neurological diseases [36, 37].

Studies have also shown that folic acid can prevent the development and eliminate endothelial dysfunction, which is an important risk factor for CVS. Vitamin B9 has the ability to increase the bioavailability of nitric oxide by increasing endothelial no synthase binding and nitric oxide production, and by direct uptake of superoxide radicals. By increasing the bioavailability of nitric oxide, folate improves endothelial function, thereby preventing or stopping the progression of CVS diseases [38-40].

Analysis of literature sources on the study of vitamin B9 in children with syncope identified only one study in this area. Thus, T. Öner *et al.* [15] identified no differences in folate scores in the groups of children with VS and healthy respondents. Given the important role of folate in the functioning of the cardiovascular and nervous systems, the need for further research on vitamin B9 in children with syncope is quite relevant and justified. Pyridoxine is another B vitamin that, as a cofactor of two cystathionine synthase enzymes, plays an important role in homocysteine metabolism, namely the conversion of homocysteine to cystathionine and cystathionase and the synthesis of cysteine from cystathionine. The absence of this cofactor leads to an increase in homocysteine levels [40].

The existence of a direct link between the level of circulating pyridoxal-5-phosphate and the development of cardiovascular diseases has been actively debated in recent decades, but the established evidence is still contradictory. While some researchers suggest that this relationship is direct [41], others claim that it is mediated and implemented through inflammatory mechanisms [42, 43]. One of the proposed pathways is kynurenine, which is involved in tryptophan metabolism. Along this pathway, pyridoxal-5-phosphate acts as a cofactor for enzymes that convert kynurenine into various compounds, including kynurenic acid, anthranilic acid, xanthurenic acid, and 3-hydroxyanthranilic acid with anti-inflammatory effects. Vitamin B6 can also inhibit inflammation through mechanisms involving Nuclear Factor-kappa B (NF-kB) and NOD-like Receptor Family Pyrin Domain Containing 3 (NLRP3) inflammation [44]. Inhibition of oxidative stress is another likely cardioprotective mechanism of vitamin B6 [45].

A prospective cohort study by J. Jeon *et al.* [46] showed that increased dietary intake of vitamin B6 was associated with a reduced risk of heart disease in Korean men, but not in Korean women. In another study involving two prospective cohorts in the Chinese population, high dietary intake of vitamin B6 was inversely proportional to the risk of all-cause mortality, including cardiovascular disease [47]. Another national population-based cohort study found that consuming higher doses of vitamin B6 in combination with folic acid is associated with lower mortality from CVS diseases [48]. On the other hand, a recent meta-analysis of several randomised controlled trials has shown that vitamin supplements, including vitamin B6, are ineffective in preventing cardiovascular diseases and their complications [49, 50].

The results of the conducted literature search give every reason to say that no studies on the study of vitamin B6 levels in children with syncope have yet been conducted. S. Blitshteyn [51] documented vitamin B1 deficiency in 6% of 65 patients with SPOT and described a substantial improvement in symptoms in one in four deficient patients after oral vitamin B1 administration. Thus, a much wider range of B vitamins than previously described may be associated with the development of syncope.

Hyperhomocysteinemia has been shown to be an independent risk factor for many diseases, including neurodegenerative and cardiovascular diseases. Despite a large body of evidence for the involvement of homocysteine in these diseases, pathophysiological mechanisms are still poorly described, complex, and multifactorial. Numerous experimental studies have shown that homocysteine can cause cellular and molecular oxidative stress through the formation of reactive oxygen forms [52, 53]. Disruption of epigenetic mechanisms to control gene expression, such as DNA methylation, histone modification, and non-coding RNA, is another possible mechanism for homocysteine toxicity. Homocysteine can alter the structure and function of proteins by binding to their lysine or cysteine residues. These mechanisms of homocysteine-mediated damage are not mutually exclusive since altered expression and post-translational modification of proteins involved in pro-oxidant/antioxidant pathways can lead to increased cellular oxidative stress, and conversely, free radicals can cause changes in gene expression and oxidative post-translational modifications of proteins [54, 55]. There is more than enough evidence that homocysteine affects mitochondrial homeostasis, including energy metabolism, mitochondrial apoptotic pathway, and mitochondrial dynamics [56].

Y. Li *et al.* [24] established that elevated plasma homocysteine concentrations in children with SPOT, which correlated with the severity of symptoms and indicated that homocysteine may be involved in the pathogenesis of SPOT. No other studies to confirm or refute the likely role of homocysteine in the development of syncope in children have yet been conducted.

THE ROLE OF VITAMIN D DEFICIENCY IN THE DEVELOPMENT OF SYNCOPE

Unlike the folate cycle, the problem of vitamin D deficiency in children with syncope is more well understood. Q. Zhang *et al.* [19] found low vitamin D levels in 60% of children with VS, which correlated with root mean square of successive differences (rMSSD) heart rate variability. The authors suggested that children with VS may experience autonomic CVS dysfunction and a decrease in vagal tone against the background of a drop in vitamin D levels in the blood. R. Zou *et al.* [18] described a high incidence of insufficient nocturnal blood pressure reduction (non-dipper) in children with VS on the background of vitamin D deficiency, which indicates the role of the latter in the violation of the circadian rhythm of blood pressure.

In another study, the prevalence of vitamin D deficiency in the group of children with VS was 73%, and substantial differences in syncope symptoms were found depending on serum levels of 25-hydroxyvitamin D (25(OH)D). The authors showed that syncope, nausea, and heavy sweating are more common in deficient children, while dizziness and darkening of the eyes are more common in children with vitamin D deficiency [16]. Y. Xiao *et al.* [17] showed that compared to healthy children, 25(OH)D levels were reduced in patients with orthostatic insufficiency, while parathyroid hormone levels did not differ. In addition, vitamin D was the only factor associated with orthostatic insufficiency – with an increase of 25(OH)D per unit, the probability of orthostatic insufficiency decreased by 77.7%.

The role of serum 25(OH)D deficiency in the development of syncope may be due to several likely mechanisms. The active form of vitamin D is thought to be one of the key factors in the proliferation and development

of vascular wall smooth muscle cells, endothelial cells, and immune system cells. The vitamin D receptor present in these cells regulates the relaxation and contraction of vascular wall smooth muscle cells through the synthesis of nitric oxide and calcium-mediated pathways [57, 58]. Thus, 25(OH)D deficiency in the blood can contribute to the development of syncope due to a decrease in peripheral vascular resistance during the pathological Bezold-Jarisch reflex.

One of the causes of syncope is a violation of the function of the heart muscle. It has been proven that strong contractions of the empty ventricle of the heart cause activation of cardiac C-fibres during the Bezold-Jarisch reflex, while vitamin deficiency is accompanied by a violation of the autonomic activity of the heart due to inhibition of vagus nerve tone [21]. In addition, vitamin D deficiency increases the risk of cardiovascular disease, heart failure, and sudden cardiac death [59, 60]. As a result, a lack of this vitamin can be considered an independent risk factor for developing heart muscle dysfunction.

Another important pathophysiological link of syncope is a violation of the neuronal conduction of the baroreflector mechanism. Vitamin D, which is also present in the central and peripheral nervous system, plays an important role in maintaining the neurotrophic and neuroprotective effects of growth factors involved in neurotransmitter conduction and nerve cell growth [61, 62]. Therefore, the risk of syncope may increase with hypovitaminosis D due to the indirect effect of 25(OH)D on the central nervous system, smooth muscle cells, and baroreceptor zones.

Therefore, all the above facts indicate the involvement of vitamin B6, B9, B12 deficiency, hyperhomocysteinemia, and 25-OH-D in the pathogenetic mechanisms of transient loss of consciousness of syncopal origin. Determination of the levels of vitamins B6, B9, B12, 25-OH-D and homocysteine in children with syncope will allow not only a better understanding of the nature of syncope but also conducting timely medical correction of detected disorders.

CONCLUSIONS

Thus, the results of recent studies suggest that homocysteine, vitamins B6, B9, B12, and D may play an indirect and in some cases direct effect in the pathogenesis of syncope. Vitamin B12 deficiency appears to play a role in the development of syncope due to the effects of delayed myelination and nerve conduction, and increased serum norepinephrine levels. It is the pathological Bezold-Jarisch reflex with a decrease in sympathetic impulses and increased vagal effects against the background of inadequate release of norepinephrine into the blood serum that is one of the key mechanisms for the development of non-cardiogenic syncope. Therefore, it is logical to assume that vitamin B12 deficiency can affect the autonomic regulation of heart activity in the same way as it occurs in VS.

Pathophysiological features of the effect of vitamin B6 and B9 deficiency on the development of syncope in children are still not examined. Probable pathogenetic mechanisms of vitamin D deficiency in the genesis of syncope are a decrease in peripheral vascular resistance, a violation of the neuronal conduction of the baroreflective mechanism, and dysfunction of the heart muscle. Scientific reports on the effects of vitamins B1, B6, and B9 on the functioning of the cardiovascular and nervous systems in children indicate that other vitamins may also be involved in the pathogenetic mechanisms of syncope development.

Despite this, data on the causal relationships between folate cycle and vitamin D indicators and syncope are mixed, contradictory, and ambiguous, are observational in nature, relate mainly to the adult population and require further research to find new pathogenetically sound methods of treatment and prevention.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Lyon P, Strippoli V, Fang B, Cimmino L. B Vitamins and one-carbon metabolism: Implications in human health and disease. Nutrients. 2020;12(9):2867. DOI: 10.3390/nu12092867
[2] Chen H, Liu S, Ge B, Zhou D, Li M, Li W, et al. Effects of folic acid and vitamin B12 supplementation on cognitive impairment and inflammation in patients with Alzheimer's disease: A randomized, single-blinded, placebo-controlled trial. J Prev Alzheimers Dis. 2021;8:249–56. DOI: 10.14283/jpad.2021.22
[3] Khosravi M, Sotoudeh G, Amini M, Raisi F, Mansoori A, Hosseinzadeh M. The relationship between dietary patterns and depression mediated by serum levels of folate and vitamin B12. BMC Psychiatry. 2020;20:63. DOI: 10.1186/s12888-020-2455-2
[4] Li WX, Cheng F, Zhang AJ, Dai SX, Li GH, Lv WW, et al. Folate deficiency and gene polymorphisms of MTHFR, MTR and MTRR elevate the hyperhomocysteinemia risk. Clin Lab. 2017;63(3):523–33. DOI: 10.7754/Clin.Lab.2016.160917
[5] Kumar A, Palfrey HA, Pathak R, Kadowitz PJ, Gettys TW, Murthy SN. The metabolism and significance of homocysteine in nutrition and health. Nutr Metab (Lond). 2017 Dec 22;14:78. PMID: 29299040; PMCID: PMC5741875. DOI: 10.1186/s12986-017-0233-z
[6] Kaye AD, Jeha GM, Pham AD, Fuller MC, Lerner ZI, Sibley GT, et al. Folic acid supplementation in patients with elevated homocysteine levels. Adv Ther. 2020;37(10):4149–64. DOI: 10.1007/s12325-020-01474-z
[7] Ueno A, Hamano T, Enomoto S, Shirafuji N, Nagata M, Kimura H, et al. Influences of vitamin B12 supplementation on cognition and homocysteine in patients with vitamin B12 deficiency and cognitive impairment. Nutrients. 2022;14(7):1494. DOI: 10.3390/nu14071494
[8] Herrmann W, Herrmann M. The controversial role of HCY and vitamin B deficiency in cardiovascular diseases. Nutrients. 2022;14(7):1412. DOI: 10.3390/nu14071412
[9] Nitsa A, Toutouza M, Machairas N, Mariolis A, Philippou A, Koutsilieris M. Vitamin D in cardiovascular disease. In Vivo. 2018;32(5):977–81.DOI: 10.21873/invivo.11338

[10] Cosentino N, Campodonico J, Milazzo V, De Metrio M, Brambilla M, Camera M, et al. Vitamin D and cardiovascular disease: current evidence and future perspectives. Nutrients. 2021;13(10):3603. DOI: 10.3390/nu13103603
[11] Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med. 2019;380(1):33–44. DOI: 10.1056/NEJMoa1809944
[12] Manson JE, Bassuk SS, Cook NR, Lee I-M, Mora S, Albert CM, Buring JE. Vitamin D, marine n-3 fatty acids, and primary prevention of cardiovascular disease: Current evidence. Circ Res. 2020;126:112–28. DOI: 10.1161/CIRCRESAHA.119.314541
[13] PRISMA Statement. PRISMA Flow Diagram. [Internet]. Available from: http://prisma-statement.org/prismastatement/flowdiagram.aspx
[14] Pektas A, Koken R, Koca HB. Serum vitamin B-12 in children presenting with vasovagal syncope. Asia Pac J Clin Nutr. 2018;27(1):176–81. DOI: 10.6133/apjcn.022017.17
[15] Öner T, Guven B, Tavli V, Mese T, Yılmazer MM, Demirpence S. Postural orthostatic tachycardia syndrome (POTS) and vitamin B12 deficiency in adolescents. Pediatrics. 2014;133(1):138–42. DOI: 10.1542/peds.2012-3427
[16] Kong YJ, Bian P, Yang YN, Dong T, Niu SM, Yuan SJ, Dong XY. Association of vitamin D deficiency with severity of symptoms in children with vasovagal syncope. Zhonghua Er Ke Za Zhi. 2022 Jun 2;60(6):557–61. DOI: 10.3760/cma.j.cn112140-20211009-00854
[17] Xiao Y, Wu J, Min L, Dong XY. The correlation between serum 25-hydroxyvitamin D and parathyroid hormone levels and orthostatic intolerance in children. Progress in Pediatric Cardiology. 2022; 66:101550. DOI: 10.1016/j.ppedcard.2022.101550
[18] Zou R, Wang S, Cai H, Li F, Lin P, Wang Y, Wang C. Vitamin D deficiency in children with vasovagal syncope is associated with impaired circadian rhythm of blood pressure. Front Neurosci. 2021;15:712462. DOI: 10.3389/fnins.2021.712462
[19] Zhang Q, Sun Y, Zhang C, Qi J, Du J. Vitamin D Deficiency and Vasovagal Syncope in Children and Adolescents. Front Pediatr. 2021;9:575923. DOI: 10.3389/fped.2021.575923
[20] Gilani A, Ramsay SE, Welsh P, Papacosta O, Lennon LT, Whincup PH, Wannamethee SG. Vitamin D deficiency is associated with orthostatic hypotension in older men: A cross-sectional analysis from the British Regional Heart Study. Age Ageing. 2021;50(1):198–4. DOI: 10.1093/ageing/afaa146
[21] Usalp S, Kemal H, Yüksek Ü, Yaman B, Günsel A, Edebal O, Akpınar O, et al. Is there any link between vitamin D deficiency and vasovagal syncope? J Arrhythmia. 2020;36(2):371–76. DOI: 10.1002/joa3.12309
[22] Hesselbrock RR, Palileo EV, Davenport ED. Vitamin B12 deficiency related syncope in a young military pilot. Aerospace Med Hum Perform. 2020;91(9):746–48. DOI: 10.3357/AMHP.5650.2020
[23] Serin HM, Arslan EA. Neurological symptoms of vitamin B12 deficiency: Analysis of pediatric patients. Acta Clin Croat. 2019;58(2). DOI: 10.20471/acc.2019.58.02.13
[24] Li Y, He B, Li H, Zhang Q, Tang C, Du J, Jin H. Plasma homocysteine level in children with postural tachycardia syndrome. Front Pediatr. 2018;6:375. DOI: 10.3389/fped.2018.00375
[25] Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. World J Diabetes. 2021;12(7):916–31. PMID: 34326945. DOI: 10.4239/wjd.v12.i7.916
[26] Ankar A, Kumar A. Vitamin B12 deficiency. In: StatPearls [Internet]. 2022 [cited 2023 Apr 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441923/
[27] Sobczyńska-Malefora A, Delvin E, McCaddon A, Ahmadi KR, Harrington DJ. Vitamin B_{12} status in health and disease: A critical review. Diagnosis of deficiency and insufficiency – clinical and laboratory pitfalls. Crit Rev Clin Lab Sci.2021;58(6):399–29. DOI: 10.1080/10408363.2021.1885339
[28] He W, Wang X, Liu S, Yu X, Lu Z, Ma R, Luo D, et al. Sympathetic mechanisms in an animal model of vasovagal syncope. Clin Auton Res. 2018;28:333–40. DOI: 10.1007/s10286-018-0503-5
[29] Stewart JM, Medow MS, Sutton R, Visintainer P, Jardine DL, Wieling W. Mechanisms of vasovagal syncope in the young: reduced systemic vascular resistance versus reduced cardiac output. J Am Heart Assoc. 2017;6:e004417. DOI: 10.1161/JAHA.116.004417
[30] Bell DSH. Metformin-induced vitamin B12 deficiency can cause or worsen distal symmetrical, autonomic and cardiac neuropathy in the patient with diabetes. Diabetes Obes Metab. 2022;24(8):1423–28. DOI: 10.1111/dom.14734
[31] Celik SF, Celik E. Subclinical atherosclerosis and impaired cardiac autonomic control in pediatric patients with Vitamin B12 deficiency. Niger J Clin Pract. 2018;21(8):1012–16. DOI: 10.4103/njcp.njcp_345_17
[32] Liu Y, Geng T, Wan Z, Lu Q, Zhang X, Qiu Z, et al. Associations of serum folate and Vitamin B12 levels with cardiovascular disease mortality among patients with type 2 diabetes. JAMA Netw Open. 2021;5(1):e2146124. DOI: 10.1001/jamanetworkopen.2021.46124
[33] Xu X, Wei W, Jiang W, Song Q, Chen Y, Li Y, et al. Association of folate intake with cardiovascular-disease mortality and all-cause mortality among people at high risk of cardiovascular-disease. Clin Nutr. 2022;41(1):246–54. DOI: 10.1016/j.clnu.2021.11.007
[34] An P, Wan S, Luo Y, Luo J, Zhang X, Zhou S, et al. Micronutrient supplementation to reduce cardiovascular risk. J Am Coll Cardiol. 2022;80(24):2269–85. DOI: 10.1016/j.jacc.2022.09.048
[35] Zhang B, Dong H, Xu Y, Xu D, Sun H, Han L. Associations of dietary folate, vitamin B6 and B12 intake with cardiovascular outcomes in 115664 participants: A large UK population-based cohort. Eur J Clin Nutr. 2023;77:299–307. DOI: 10.1038/s41430-022-01206-2

[36] Bo Y, Zhu Y, Tao Y, Li X, Zhai D, Bu Y, et al. Association between folate and health outcomes: An umbrella review of meta-analyses. Front Publ Health. 2020;15(8):550753. DOI: 10.3389/fpubh.2020.550753
[37] Sanderson SM, Gao X, Dai Z, Locasale JW. Methionine metabolism in health and cancer: A nexus of diet and precision medicine. Nature Reviews. Cancer. 2019;19(11):625–37. DOI: 10.1038/s41568-019-0187-8
[38] Yuyun MF, Ng LL, Ng GA. Endothelial dysfunction, endothelial nitric oxide bioavailability, tetrahydrobiopterin, and 5-methyltetrahydrofolate in cardiovascular disease. Where are we with therapy? Microvasc Res.2018;119:7–12. DOI: 10.1016/j.mvr.2018.03.012
[39] Haloul M, Vinjamuri SJ, Naquiallah D, Mirza MI, Qureshi M, Hassan C, et al. Hyperhomocysteinemia and low folate and vitamin B12 are associated with vascular dysfunction and impaired nitric oxide sensitivity in morbidly obese patients. Nutrients. 2020;12(7):2014. DOI: 10.3390/nu12072014
[40] Stach K, Stach W, Augoff, K. Vitamin B6 in health and disease. Nutrients. 2021;13(9):3229. DOI: 10.3390/nu13093229
[41] Kumrungsee T, Zhang P, Yanaka N, Suda T, Kato N. Emerging cardioprotective mechanisms of vitamin B6: A narrative review. Eur J Nutr. 2022;61(2):605–13. DOI: 10.1007/s00394-021-02665-2
[42] Minović I, Kieneker LM, Gansevoort RT, Eggersdorfer M, Touw DJ, Voerman AJ, et al. Vitamin B6, inflammation, and cardiovascular outcome in a population-based cohort: The prevention of renal and vascular end-stage disease (PREVEND) Study. Nutrients. 2020;12(9):2711. DOI: 10.3390/nu12092711
[43] Pusceddu I, Herrmann W, Kleber ME, Scharnagl H, Hoffmann MM, Winklhofer-Roob BM, et al. Subclinical inflammation, telomere shortening, homocysteine, vitamin B6, and mortality: The ludwigshafen risk and cardiovascular health study. Eur J Nutr.2020;59(4):1399–11. DOI: 10.1007/s00394-019-01993-8
[44] Orsatti L, Stiehl T, Dischinger K, Speziale R, Di Pasquale P, Monteagudo E, et al. Kynurenine pathway activation and deviation to anthranilic and kynurenic acid in fibrosing chronic graft-versus-host disease. Cell Rep Med. 2021;2(10):100409. DOI: 10.1016/j.xcrm.2021.100409
[45] Ford TC, Downey LA, Simpson T, McPhee G, Oliver C, Stough C. The effect of a high-dose vitamin B multivitamin supplement on the relationship between brain metabolism and blood biomarkers of oxidative stress: A randomized control trial. Nutrients. 2018;10(12):1860. DOI: 10.3390/nu10121860
[46] Jeon J, Park K. Dietary vitamin B_6 Intake associated with a decreased risk of cardiovascular disease: A prospective cohort study. Nutrients. 2019;11(7):1484. DOI: 10.3390/nu11071484
[47] Zhao LG, Shu XO, Li HL, Gao J, Han LH, Wang J, et al. Prospective cohort studies of dietary vitamin B6 intake and risk of cause-specific mortality. Clin Nutr. 2019;38(3):1180–87. DOI: 10.1016/j.clnu.2018.04.016
[48] Bo Y, Xu H, Zhang H, Zhang J, Wan Z, Zhao X, Yu Z. Intakes of folate, vitamin B6, and vitamin B12 in relation to all-cause and cause-specific mortality: A national population-based cohort. Nutrients. 2022;14(11):2253. DOI: 10.3390/nu14112253
[49] Jenkins DJA, Spence JD, Giovannucci EL, Kim YI, Josse R, Vieth R, et al. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol. 2018;71(22):2570–84. DOI: 10.1016/j.jacc.2018.04.020
[50] Kim J, Choi J, Kwon SY, McEvoy JW, Blaha MJ, Blumenthal RS, et al. Association of multivitamin and mineral supplementation and risk of cardiovascular disease: A systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2018;11(7):e004224. DOI: 10.1161/CIRCOUTCOMES.117.004224
[51] Blitshteyn S. Vitamin B1 deficiency in patients with postural tachycardia syndrome (POTS). Neurol Res. 2017;39(8):685–88. DOI: 10.1080/01616412.2017.1331895
[52] Moretti R, Caruso P. The controversial role of homocysteine in neurology: From labs to clinical practice. Int J Mol Sci. 2019;20(1):231. DOI: 10.3390/ijms20010231
[53] You ZP, Zhang YZ, Zhang YL, Shi L, Shi K. Homocysteine induces oxidative stress to damage trabecular meshwork cells. Exp Ther Med. 2018;15(5):4379–85. DOI: 10.3892/etm.2018.5961
[54] Jakubowski H. Homocysteine modification in protein structure/function and human disease. Physiol Rev. 2019;99(1):555–4. DOI: 10.1152/physrev.00003.2018
[55] Wang WM, Jin HZ. Homocysteine: A potential common route for cardiovascular risk and DNA methylation in psoriasis. Chin Med J (Engl). 2017;130(16):1980–86. DOI: 10.4103/0366-6999.211895
[56] Kaplan P, Tatarkova Z, Sivonova MK, Racay P, Lehotsky J. Homocysteine and mitochondria in cardiovascular and cerebrovascular systems. Int J Mol Sci. 2020;21(20):7698. DOI: 10.3390/ijms21207698
[57] Zhou W, Wang W, Yuan XJ, Xiao CC, Xing Y, Ye SD, Liu Q. The effects of RBP4 and vitamin D on the proliferation and migration of vascular smooth muscle cells via the JAK2/STAT3 signaling pathway. Oxid Med Cell Longev. 2022;3046777. DOI: 10.1155/2022/3046777
[58] Surdu AM, Pînzariu O, Ciobanu DM, Negru AG, Căinap SS, Lazea C, et al. Vitamin D and its role in the lipid metabolism and the development of atherosclerosis. Biomedicines. 2021;9(2):172. DOI: 10.3390/biomedicines9020172
[59] Wu M, Xu K, Wu Y, Lin L. Role of vitamin D in patients with heart failure with reduced ejection fraction. Am J Cardiovasc Drugs. 2019;19(6):541–52. DOI: 10.1007/s40256-019-00357-1
[60] Ozer PK, Emet S, Karaayvaz EB, Elitok A, Bilge AK, Adalet K, Oncul A. Silent myocardial dysfunction in vitamin D deficiency. Atheroscler Dis. 2020;5(1):153–62. DOI: 10.5114/amsad.2020.97110
[61] Gombash SE, Lee PW, Sawdai E, Lovett-Racke AE. Vitamin D as a risk factor for multiple sclerosis: Immunoregulatory or neuroprotective? Front Neurol. 2022;(13):796933. DOI: 10.3389/fneur.2022.796933
[62] Kaviani M, Nikooyeh B, Zand H, Yaghmaei P, Neyestani TR. Effects of vitamin D supplementation on depression and some involved neurotransmitters J Affect Disord. 2020;269:28–35. DOI: 10.1016/j.jad.2020.03.029

Патофізіологічні основи порушень фолатного циклу та дефіциту вітаміну D у розвитку синкопе в дитячому віці

Тетяна Анатоліївна Ковальчук
Кандидат медичних наук, доцент
Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України
46001, майдан Волі, 1, м. Тернопіль, Україна
https://orcid.org/0000-0003-2455-3278
Оксана Романівна Боярчук
Доктор медичних наук, професор
Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України
46001, майдан Волі, 1, м. Тернопіль, Україна
https://orcid.org/0000-0002-1234-0040

Анотація. Існує чимало повідомлень щодо ролі вітамінів B6, B9, B12 та D у розвитку серцево-судинних захворювань. Однак, більшість із них стосуються головним чином дорослого населення і є досить лімітованими щодо оцінок у дітей із синкопе. Розуміння ролі цих вітамінів в патогенезі непритомності допоможе розширити комплекс лікувально-профілактичної допомоги дітям. Метою дослідження був аналіз сучасних наукових досягнень щодо ролі фолатного циклу та вітаміну D у генезі синкопе в дитячому віці. Були використані бази даних PubMed Medline і Scopus та застосовані наступні пошукові терміни: «синкопе» та «вітамін B»; «синкопе» та «гомоцистеїн»; «синкопе» та «вітамін D». В роботі узагальнено роль дефіциту вітаміна B12 у сповільненій мієлінізації та нервовій провідності, підвищенні рівня норадреналіну в сироватці крові, як імовірних патогенетичних механізмів розвитку некардіогенних синкопе. Описані наукові факти впливу вітамінів B1, B6, B9 на функціонування серцево-судинної та нервової систем у дітей. Було встановлено поширеність дефіциту вітаміна D у 60-73% дітей із вазовагальними синкопе та його взаємозв'язки з симптомами хвороби. Проаналізовані ймовірні патогенетичні механізми нестачі вітаміна D у розвитку синкопе, а саме зниження периферичного опору судин, порушення нейрональної провідності барорефлекторного механізму, дисфункція серцевого м'яза. Отримані результати дозволять лікарям та науковцям більш ефективно підходити до діагностики, профілактики та лікування синкопе у дитячому віці та можуть служити основою для розробки нових стратегій управління цим станом та вдосконалення медичної практики

Ключові слова: вітаміни; гомоцистеїн; вазовагальні синкопе; синкопе внаслідок ортостатичної гіпотензії; кардіогенні синкопе; діти