Received: 21 March 2023 / Accepted: 12 April 2023 / Published online: 30 April 2023

DOI 10.34689/SH.2023.25.2.011

UDC 340.624.41:577.164.1

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY ANALYSIS OF PLASMA LEVELS OF VITAMINS GROUP «B» IN METABOLIC SYNDROME

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Abstract

Background: Examining blood plasma for B vitamins can be pivotal in detecting metabolic syndrome (MetS), a group of risk factors that raise the likelihood of acquiring cardiovascular disease and type 2 diabetes. B vitamins, namely thiamine (B1), riboflavin (B2), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate (B9), and cobalamin (B12), are critical for multiple metabolic functions in the body, such as generating energy, synthesizing DNA, and maintaining nerve function. Inadequate levels or uneven ratios of these B vitamins can contribute to the onset and advancement of MetS.

Objective: To detect variations in the levels of B vitamins (B1, B2, B5, B6, B7, B9, and B12) in the blood plasma of patients with MetS by High-Performance Liquid Chromatography (HPLC).

Materials and methods: Fifteen patients who have been diagnosed with MetS and meet the relevant criteria were selected, and samples of their plasma were collected to determine the levels of vitamin B1, B2, B5, B6, B7, B9, and B12 by HPLC. Additionally, plasma samples were also collected and analyzed from fifteen apparently healthy individuals. The samples were evaluated for their concentration levels of vitamins B i group n patients with MetS and apparently healthy individuals.

Results and discussion: The study findings demonstrated a significant decrease of plasma levels of vitamins B1 and B9 in patients with MetS compared with healthy individuals, whereas plasma levels of vitamin B12 were twice as high as control group. To evaluate the modified method and customize the previously developed assay technique to the specific needs of blood testing, a relatively larger sample size is required to confirm these findings.

Keywords: *metabolic syndrome, B vitamins, HPLC.*

Резюме

ВЫСОКОЭФФЕКТИВНЫЙ ЖИДКОСТНЫЙ ХРОМАТОГРАФИЧЕСКИЙ АНАЛИЗ В ОПРЕДЕЛЕНИИ УРОВНЯ ВИТАМИНОВ ГРУППЫ «В» В ПЛАЗМЕ КРОВИ ПРИ МЕТАБОЛИЧЕСКОМ СИНДРОМЕ

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Актуальность: Исследование плазмы крови на наличие витаминов группы В может иметь решающее значение для выявления метаболического синдрома (МС), группы факторов риска, повышающих вероятность развития сердечно-сосудистых заболеваний и диабета 2 типа. Витамины группы В, а именно тиамин (В1), рибофлавин (В2), пантотеновая кислота (В5), пиридоксин (В6), биотин (В7), фолиевая кислота (В9),и кобаламин (В12), имеют решающее значение для многих метаболических функций в организме, таких как выработка энергии, синтез ДНК и поддержание функции нервной системы. Неадекватные уровни или неравномерное соотношение этих витаминов группы В могут способствовать возникновению и прогрессированию МС.

Цель: выявить вариации уровней витаминов группы В (В1, В2, В5, В6, В7, В9 и В12) в плазме крови пациентов с метаболическим синдромом с помощью высокоэффективной жидкостной хроматографии (ВЭЖХ).

Материалы и методы. Были отобраны пятнадцать пациентов с МС, соответствующих критериям включения в исследование и пятнадцать здоровых лиц для определения уровней витаминов группы «В»: В1, В2, В5, В6, В7, В9 и В12 с помощью ВЭЖХ. Были собраны и проанализированы образцы плазмы по уровню концентрации витаминов группы «В» у пациентов с МС и здоровых лиц.

Результаты и обсуждение. Результаты исследования показали, что у лиц с МС значительно снижен уровень в крови витаминов В1 и В9, тогда как концентрация В12 была значительно выше, чем в контрольной группе. Чтобы оценить модифицированный метод и адаптировать ранее разработанный метод анализа к конкретным потребностям анализа крови, для подтверждения этих результатов требуется относительно больший размер выборки.

Ключевые слова: *метаболический синдром, витамины группы В, ВЭЖХ.*

Түйіндеме

МЕТАБОЛИЗМ СИНДРОМЫ ЖАҒДАЙЫНДАҒЫ «В» ТОБЫНДАҒЫ ВИТАМИНДЕР ДЕҢГЕЙІН АНЫҚТАУ ҮШІН ЖОҒАРЫ ТИІМДІЛІК СҰЙЫҚ ХРОМАТОГРАФИЯЛЫҚ ТАЛДАУ

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Өзектілігі: Қан плазмасы құрамындағы В витаминдер деңгейін зерттеу метаболизм синдромын (МС), жүрек-тамыр аурулары мен 2 типті қант диабетінің даму ықтималдығын арттыратын қауіп факторларының тобын анықтауда маңызды болуы мүмкін. В тобының витаминдері, атап айтқанда тиамин (В1), рибофлавин (В2), пантотен қышқылы (В5), пиридоксин (В6), биотин (В7), фолий қышқылы (В9) және кобаламин (В12), энергия өндіру, ДНҚ синтезі және жүйке жүйесі қызметтерін ынталандыру сияқты ағзадағы көптеген метаболизм функциялары үшін өте маңызды. Осы В витаминдерінің жеткіліксіз деңгейі немесе біркелкі емес арақатынасы метаболизм синдромының пайда болуына және өршуіне ықпал етуі мүмкін.

Мақсаты: жоғары нәтижелі сұйық хроматография (ЖНСХ) әдісімен метаболизм синдромы бар науқастардың қан плазмасындағы В витаминдері (В1, В2, В5, В6, В7, В9 және В12) деңгейінің вариациясын анықтау.

Материалдар мен тәсілдер. Зерттеуге қосуға критерийлерге сай **м**етаболизм синдромы диагнозы анықталған 15 жарамды пациент және дені сау 15 адам ЖНСХ әдісімен В тобындағы (В1, В2, В5, В6, В7, В9, В12) витаминдер деңгейлерін анықтау үшін тандалды. Метаболизм синдромы бар науқастар мен сау адамдардың В витаминдер концентрациясы деңгейлері бойынша қан плазмасы үлгілері алынып, зерттелді.

Нәтижелер мен талдаулар. Зерттеу нәтижелері метаболизм синдромы бар адамдарда В2, В12 және В6 витаминдерінің қандағы деңгейі айтарлықтай жоғарылағанын, ал В9 витамині концентрациясы бақылау тобына қарағанда айтарлықтай төмен екенін көрсетті. Модификацияланған әдісті бағалау және бұрын әзірленген талдау әдісін қан сынауының нақты қажеттіліктеріне бейімдеу үшін осы нәтижелерді растау үшін салыстырмалы түрде зерттелуші адамдар саны үлкенірек зерттеулер қажет.

Түйінді сөздер: *метаболизм синдромы, В витаминдері, ЖНСХ.*

Bibliographic citation:

Nurtazina A., Toishimanov M., Voitsekhovskiy I., Dautov D. High Performance Liquid Chromatography Analysis of Plasma Levels of Vitamins Group «B» in Metabolic Syndrome // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2023, (Vol.25) 2, pp. 79-83. *doi 10.34689/SH.2023.25.2.011*

Нуртазина А., Тойшиманов М., Войцеховский И., Даутов Д. Высокоэффективный жидкостный хроматографический анализ в определении уровня витаминов группы «В» в плазме крови при метаболическом синдроме // Наука и Здравоохранение. 2023. 2(Т.25). С. 79-83. *doi 10.34689/SH.2023.25.2.011*

Нуртазина А., Тойшиманов М., Войцеховский И., Даутов Д. Метаболизм синдромы жағдайындағы «В» тобындағы витаминдер деңгейін анықтау үшін жоғары тиімділік сұйық хроматографиялық талдау // Ғылым және Денсаулық сақтау. 2023. 2 (Т.25). Б. 79-83. *doi 10.34689/SH.2023.25.2.011*

Background:

Metabolic syndrome (MetS) encompasses a range of pathological conditions, such as central and abdominal obesity, insulin resistance, arterial hypertension, and dyslipidemia. MetS is commonly observed in individuals with morbid obesity and is linked to a 5-fold risk of type 2 diabetes and a 2-fold risk of cardiovascular complications [1]. The presence of MetS in the general population is associated with early carotid atherosclerosis, indicating that it plays a significant role in the initiation of the atherosclerotic process [2]. The rapid rise in the prevalence of MetS has made it a global health issue. Although the precise mechanisms leading to the development of MetS are not yet entirely understood, visceral adiposity and an increase in very-low-density lipoprotein and fatty acid synthesis are believed to be key contributing factors. While pharmaceutical therapies are available to address the individual components of MetS, the relationship between MetS and the supplementation of B vitamins, specifically folic acid and vitamin B12, has received worldwide attention, with numerous trials examining the potential benefits of vitamin supplementation for MetS. According to research, vitamin B12 and folate supplementation, alongside a variety of innovative therapies, have a significant positive impact on MetS [3].

The folate cofactor (vitamin B9) mediates one-carbon (1C) metabolism, which supports various physiological processes [4]. One-carbon (1C) metabolism is a complex system of metabolic pathways that includes the methionine and folate cycles, both of which are critical to cellular function. These pathways provide 1C units (methyl groups) that are essential for synthesizing DNA, amino acids, polyamines, creatine, and phospholipids, among other things [5]. The interlinking metabolic pathways involved in one-carbon (1C) metabolism, including the methionine and folate cycles [6]. Disruption of these cycles due to a deficit in vitamin B12 and/or folate can have downstream effects on cellular processes that require 1C units [7].

Riboflavin (vitamin B2)-dependent enzymes, methylenetetrahydrofolate reductase (MTHFR), and methionine synthase reductase (MTRR) participate in homocysteine metabolism [8].

Low levels of vitamin B12 and folic acid can result in mild hyperhomocysteinemia, which is a proven cardiovascular risk marker. Decreased levels of vitamin B2, vitamin B12, and folic acid have been observed in both obesity and metabolic syndrome groups, and hypertensive patients have been found to have significantly lower folate plasma concentrations compared to control subjects [9]. Blood plasma analysis for B vitamins can aid in the diagnosis of metabolic syndrome, a cluster of risk factors that increase the likelihood of developing cardiovascular disease and type 2 diabetes. B vitamins, including vitamin B6, vitamin B9, and vitamin B12, are crucial for various metabolic processes in the body, such as energy production, DNA synthesis, and nerve function, and deficiencies or imbalances in these B vitamins can contribute to the development and progression of MetS.

2. Materials and methods

2.1 Ethics statement

Before participating in this study, all individuals were asked to provide written informed consent, and the study protocol received approval from the Local Ethical Committee of Semey Medical University.

2.2 Study subjects

A total of 30 individuals residing in Almaty city and surrounding areas were randomly recruited for a comprehensive analysis of B vitamins (B1, B2, B5, B6, B7, B9, B12) levels in their blood plasma. Out of the 30 participants, 15 female subjects diagnosed with MetS were randomly selected from one of outpatient clinics in Almaty city. These participants were confirmed to have MetS based on the presence of at least three of the following criteria: resting blood pressure ≥130/85 mmHg, fasting serum triglycerides ≥1.7 mmol/L, high-density lipoprotein cholesterol (HDL-C) <1.30 mmol/L in females and 1.03 mmol/L in males, fasting plasma glucose ≥5.6 mmol/L, and waist circumference ≥94 cm in males and ≥80 cm in females. In contrast, the control group was composed of nine women and six men who were deemed to be healthy and of normal weight. Prior to the study, all participants were informed of the procedures and provided their written consent to participate. The study was approved by the Local Ethical Committee of Semey Medical University.

2.3 Blood samples

Blood samples were taken from study participants in the morning between 7 am and 10 am, following a standardized fasting period. The samples were collected using EDTA K3 vacutainer tubes, and plasma was separated from the whole blood. To ensure the integrity of the samples, the plasma was stored at -70°C within four hours of collection and kept frozen for a period of two weeks to two months until the analysis of plasma B vitamins was conducted.

2.4 Sample Preparation

Upon thawing, plasma samples were subjected to preparation using HPLC grade acetonitrile in a 1:1 (v/v) ratio, with 300 µl of the solvent added to 300 µl of the plasma sample. The mixture was then thoroughly shaken and subsequently centrifuged at 14000×g for 10 minutes, with the temperature maintained at 4 ◦C. Following centrifugation, 300 µl of the supernatant was carefully collected and transferred to vials for subsequent HPLC analysis.

2.5. Chromatographic system

In this study, a Shimadzu LC-20AD Prominence HPLC Pump dual piston, column oven CTO-30A, and SPD-20A dual-wavelength mode UV-VIS Detector were utilized as the HPLC system. The separation of Vitamin B complex was achieved through the use of two mobile phases. The first mobile phase, mobile phase A, was composed of 100% HPLC grade acetonitrile while mobile phase B was a mixture of 99.9% HPLC grade water, 0.1% phosphoric acid, and 25 mmol sodium dihydrogen phosphate. Prior to use, all buffers underwent filtration through a 0.2-µm filter and were degassed.

The HPLC system used for the chromatographic separation was a Shimadzu Prominence LC-20 system (Shimadzu, Japan) that was equipped with a UV detector (SPD-20A) and a fluorescent detector (RF-10AXL). Additionally, the HPLC system was fitted with a binary pump (LC-20AD), an autosampler (SIL-20AC), a degasser (DGU-20A5), and a column oven (CTO-20A) that were controlled by LC Solution. To separate samples, a Supelco Ascentis C18 HPLC column (250 mm × 4.6 mm, 5 µm) was used.

The UV detection was carried out at 210nm, and the flow rate of the mobile phase was set at 0.5 ml/min with gradient elution: 0 min – 100% B; 0-10 min – 70% B, 10-25 min – 100% B. The total HPLC run time for the separation of the Vitamin B complex in a single sample or standard was 25 min.

The method utilized to determine the levels of Vitamin B in body fluids and plants was previously developed at the Food and Environmental Safety Laboratory of the Kazakhstan-Japan Innovation Center KazNARU.

2.6 Calculations and statistics

Statistical analysis was conducted to determine whether there were significant differences between two sets of vitamins B data, using the Mann-Whitney test for independent samples. All calculations were carried out using IBM SPSS version 23.0 and JMP version 7.0 for Windows (JMP Statistical Discovery LLC, www.jmp.com).

3. Results and discussion

In this study, a quantitative analysis of seven B vitamins, namely vitamin B1, B2, B5, B6, B7, B9 and vitamin B12, was performed on 21-30 samples of blood plasma.

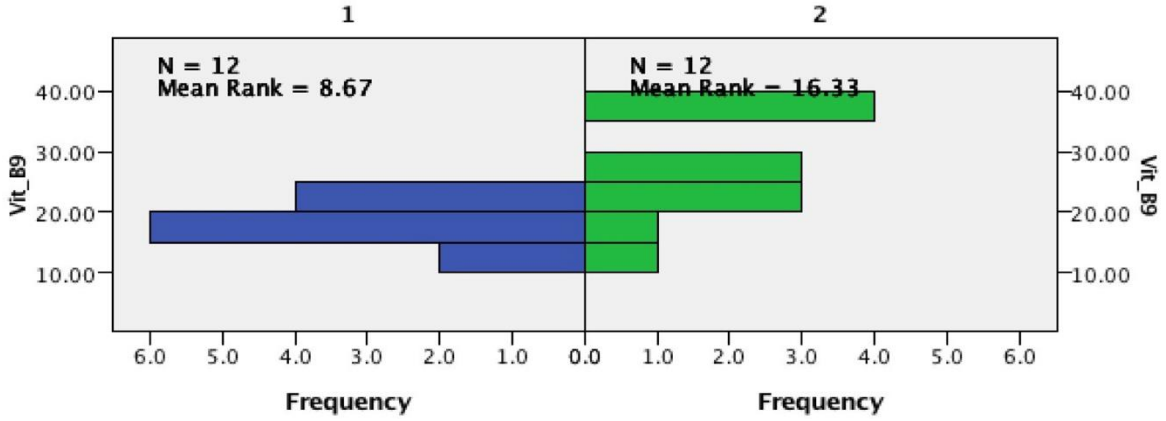
The findings demonstrate a notable contrast in plasma levels of vitamins B between the two cohorts. (Table 1).

Table 1.

Comparison of plasma levels of vitamins group B between patients with MetS and apparently healthy subjects*.

	B1	B2	B5	B6	B7	B9	B12
Total Number	25	21	22	26	26	24	25
Mann-Whitney U	43.000	28.000	44.000	73.500	118.000	118.000	4.000
Test Statistic	43.000	28.000	44.000	73.500	118.000	118.000	4.000
Standard Error	8.165	14.067	15.229	19.497	19.500	17.231	8.485
Exact Sig. (2-sided test)	.028	.069	.300	.579	.091	.007	.005

Picture 1. Vitamin B9 levels in patients with MetS and apparently healthy subjects*



1-

patients with MetS; 2 – apparently healthy subjects

***Mann-Whitney test, p=0.007**

The present study unveiled a significant difference in the values of B1, B9 and B12 between the MetS and control groups.

Vitamin B1 (thiamine) plays a critical role in carbohydrate metabolism through TPP (thiamine pyrophosphate) as an indispensable cofactor for pyruvate dehydrogenase. Without TPP, the entry into the Krebs cycle is blocked, leading to lactate accumulation. TPP is also an essential cofactor of the enzymes α-ketoglutarate dehydrogenase for conversion to succinyl CoA in the Krebs cycle and Transketolase in the pentose phosphate pathway for energy production [10] Previous studies established that thiamine levels were lower in metabolic syndrome subjects than in controls [11][12][13].

Folate from diet or supplements can donate a carbon group to homocysteine, which can be either methylated into methionine or degraded into cysteine, with vitamins B6 and B12 serving as essential coenzymes [14].

Although homocysteine (Hcy) levels were not analyzed in this study, high plasma homocysteine levels are known to be independently associated with MetS. Elevated total homocysteine levels and low folate levels, but not vitamin B12 levels, are significantly associated with hypertension [15]. Vitamin B12 deficiency is prevalent in type 2 diabetes patients and is associated with adverse lipid parameters [16]. In the obesity and MetS groups, significantly decreased levels of vitamin E, vitamin B2, vitamin B12, and folic acid, and increased levels of vitamin B1 were observed [17]. Folate serum concentration was negatively correlated with plasma homocysteine [18]. Hcy is an intermediate compound in methionine metabolism, and the remethylation of Hcy is promoted by vitamin B12 and folate in one-carbon metabolism.

Vitamin B9 plays a crucial role in the conversion of homocysteine (Hcy) to cystathionine. In cases where there is a deficiency of folate, vitamin B12, or vitamin B6, hyperhomocysteinemia may develop. This condition is characterized by elevated levels of Hcy, which in turn leads to an increase in the concentration of S-adenosylhomocysteine (SAH). High levels of SAH can inhibit methylation reactions that rely on S-adenosylmethionine (SAM) [19]. Low serum vitamin B12 levels are independently associated with abnormal lipid profiles in healthy individuals. [20]. However, earlier studies have shown an age-dependent increase in vitamin B12 in the blood. The slight upward trend in serum levels of the vitamins B12, along with the findings of a study on vitamin intake among the elderly, confirms that most older adults supplement their diet with vitamins [21].

The method for determining fluctuations in the level of B vitamins in the blood plasma of patients with MetS by HPLC had previously been developed for other biological objects, and it was necessary to modify it to suit the specific requirements of blood analysis. The sample size used in this study was 30, which is considered insufficient. Further studies with a relatively larger sample sizes are required to confirm our findings.

Acknowledgement

Declaration of conflicting interests: *The authors declare that there is no conflict of interest in the present study.*

Funding: *This research is funded by the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan (Grant No. AP14871855).*

Author contribution statement: *All authors have contributed equally.*

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