

# Prognostic value of homocysteine and vitamin D for patients with ischemic heart disease and multifocal atherosclerosis

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Cardiovascular system diseases (CSD) – is one of the most acute medical and social problems of modern society. Ischemic heart disease (IHD) and acute disturbance of cerebral circulation were and remain the leading cause of death and disability.

At present, it has been established that in the progression of IHD and its complications, an increase in the level of homocysteine and deficiency of vitamin D are essential.

**Purpose of the study:** to study the effect of hyperhomocysteinemia and deficiency of vitamin D on the course of atherosclerosis and ischemic heart disease.

**Materials and methods.** The study analyzed laboratory data from 58 patients with atherosclerosis. Depending on the prevalence of atherosclerosis patients were divided into 2 groups. All those examined had vitamin D deficiency, as well as hyperhomocysteinemia. These changes were more pronounced in patients with multifocal atherosclerosis, which required a more thorough medication correction after surgical intervention on the coronary and carotid arteries.

**Results:** Of practical interest is the analysis of blood plasma homocysteine concentration values depending on the localization of atherosclerotic lesion. In our study, in the first group, the median plasma homocysteine concentration was significantly higher. Moreover, there was a strong correlation between high concentrations of homocysteine and advanced atherosclerotic lesions. These results may indicate a possible destabilization of atherosclerosis course with hyperhomocysteinemia in combination with vitamin D deficiency.

Patients of the first group with multifocal atherosclerosis had significantly higher homocysteine indices and a more pronounced vitamin D deficiency. No less important is the fact that in the examined patients both in one group and in the other group a significant vitamin D deficiency was detected.

**Conclusions.** Hyperhomocysteinemia and vitamin D deficiency – are risk factors for the development of coronary heart disease and are associated with an unfavorable course of coronary pathology. All patients with ischemic heart disease had vitamin D deficiency and hyperhomocysteinemia, more pronounced with multifocal atherosclerosis, which should be considered when prescribing medication after myocardial revascularization.

## Key words:

myocardial ischemia, homocysteine, hyperhomocysteinemia, vitamin D, dyslipoproteinemia.

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## Прогностичне значення рівнів гомоцистеїну та вітаміну D у хворих на ІХС і мультифокальний атеросклероз

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Захворювання серцево-судинної системи (ЗССС) – одна з найгостріших медичних і соціальних проблем сучасного суспільства. Ішемічна хвороба серця (ІХС) і гостре порушення мозкового кровообігу залишаються основною причиною смертності та інвалідності.

На сьогодні встановлено, що у прогресуванні ІХС та її ускладнень істотне значення мають підвищення рівня гомоцистеїну та дефіцит вітаміну D.

**Мета роботи** – вивчити вплив гіпергомоцистеїнемії та дефіциту вітаміну D на перебіг атеросклерозу та ІХС.

**Матеріали та методи.** Здійснили аналіз лабораторних даних 58 пацієнтів, які страждають на атеросклероз. Залежно від поширеності атеросклерозу пацієнтів поділили на 2 групи. У всіх обстежених виявили дефіцит вітаміну D, а також гіпергомоцистеїнемію. Відзначені зміни були суттєво виражені в пацієнтів із мультифокальним атеросклерозом, що потребувало ретельнішої медикаментозної корекції після ревазуляризації міокарда.

**Результати.** Практичний інтерес представляє проведений аналіз значень концентрацій гомоцистеїну плазми крові залежно від ступеня та площі атеросклеротичного ураження. У нашій роботі в осіб із мультифокальним атеросклерозом (1 група) медіана концентрації гомоцистеїну плазми крові була вірогідно вищою. Нами виявлена чітка залежність між рівнем вмісту гомоцистеїну та поширеністю атеросклеротичного ураження. Ці результати свідчать про можливу дестабілізацію перебігу атеросклерозу при гіпергомоцистеїнемії в поєднанні з дефіцитом вітаміну D.

Пацієнти першої групи з мультифокальним атеросклерозом мали вірогідно вищі показники гомоцистеїну та суттєво виражений дефіцит вітаміну D. Водночас дефіцит вітаміну D виявлений у хворих обох груп.

**Висновки.** Гіпергомоцистеїнемія, дефіцит вітаміну D – фактори ризику розвитку ІХС та асоційовані з несприятливим перебігом коронарної хвороби. У всіх пацієнтів з ІХС виявлені дефіцит вітаміну D і гіпергомоцистеїнемія, більш виражені при мультифокальному атеросклерозі, що слід враховувати під час призначення медикаментозної терапії після ревазуляризації міокарда.

## Ключові слова:

ішемічна хвороба серця, гомоцистеїн, гіпергомоцистеїнемія, вітамін D загальний, дисліпопротеїнемія.

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**Ключевые слова:**

ишемическая  
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гипергомо-  
цистеинемия,  
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## Прогностическое значение уровней гомоцистеина и витамина Д у больных ИБС и мультифокальным атеросклерозом

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Заболевания сердечно-сосудистой системы (ЗССС) – одна из острых медицинских и социальных проблем современного общества. Ишемическая болезнь сердца (ИБС) и острое нарушение мозгового кровообращения остаются основной причиной смертности и инвалидности. В настоящее время установлено, что в прогрессировании ИБС и ее осложнений существенное значение имеют повышение уровня гомоцистеина и дефицит витамина Д.

**Цель работы** – изучить влияние гипергомоцистеинемии и дефицита витамина Д на течение атеросклероза и ИБС.

**Материалы и методы.** Провели анализ лабораторных данных 58 пациентов, страдающих атеросклерозом. В зависимости от распространенности атеросклероза пациентов распределили на 2 группы. У всех обследованных выявлен дефицит витамина Д, а также гипергомоцистеинемия. Указанные изменения были более выражены у пациентов с мультифокальным атеросклерозом, что требовало более тщательной медикаментозной коррекции после реваскуляризации миокарда.

**Результаты.** Практический интерес представляет проведенный анализ значений концентраций гомоцистеина плазмы крови в зависимости от степени и площади атеросклеротического поражения. В нашей работе у лиц с мультифокальным атеросклерозом (1 группа) медиана концентрации гомоцистеина плазмы крови была достоверно выше. Нами выявлена четкая зависимость между уровнем содержания гомоцистеина и распространенностью атеросклеротического поражения. Эти результаты свидетельствуют о возможной дестабилизации течения атеросклероза при гипергомоцистеинемии в сочетании с дефицитом витамина Д. Пациенты 1 группы с мультифокальным атеросклерозом имели достоверно более высокие показатели гомоцистеина и более выраженный дефицит витамина Д. В то же время дефицит витамина Д был выявлен у больных обеих групп.

**Выводы.** Гипергомоцистеинемия, дефицит витамина Д являются факторами риска развития ИБС и ассоциированы с неблагоприятным течением коронарной болезни. У всех пациентов ИБС был выявлен дефицит витамина Д и гипергомоцистеинемия, более выраженные при мультифокальном атеросклерозе, что следует учитывать при назначении медикаментозной терапии после реваскуляризации миокарда.

## Introduction

Due to ongoing population studies, the number of possible cardiovascular risk factors continues to increase. In the proof, along with hypertension, diabetes mellitus, dyslipoproteinemia and smoking, hyperhomocysteinemia is currently included, the significance of which is determined in the development of IHD and its complications, as well as atherosclerotic lesions of carotid and peripheral arteries [1,2].

For the first time data on homocysteine (HC) as a factor of atherogenesis were published in 1969 by K. S. McCully, who reported the presence of atherosclerotic lesions in patients with homocysteinuria and put forward a theory of pathogenetic link between atherosclerosis and homocysteinemia existence [3].

An increased level of homocysteine as an independent risk factor for cardiovascular disease was considered back in the 1990s. In a meta-analysis published in 1995 in the journal JAMA, which presented data from 27 studies involving more than 4,000 patients, it was concluded that homocysteine is an independent risk factor for cardiovascular disease [6,7,9]. The most common and possible mechanism for increasing the risk of developing IHD in hyperhomocysteinemia is endothelial dysfunction, which is believed to occur mainly as a result of oxidative stress [7–9].

It is also believed that the mechanisms of homocysteine damaging effect on the vascular wall are similar to those proposed for low-density lipoproteins (LDL) and are realized mainly through the induction of endothelium-dependent hemostasis dysfunction and the severe disturbance of vasodilation endothelium-mediated component, as well as the stimulation of smooth muscle cells proliferation [3].

In connection with this, the search for the relationships

between hyperhomocysteinemia and various forms of IHD, including an assessment of its significance in an atherosclerotic plaque destabilization, that manifests clinically by the acute coronary syndrome development, is of considerable interest, first of all, from the point of view of medicamentous effect substantiation on homocysteine increased concentration in such patients [3,4].

In the literature there are reports of adverse effects of hyperhomocysteinemia on the results of surgical and endovascular myocardial revascularization.

Homocysteine has a multicomponent pathogenetic effect. It damages the tissue structures of the arteries, initiating the release of cytokines, cyclins and other mediators of inflammation [10].

Epidemiological and experimental studies have shown that a low level of vitamin D plays a negative role in cardiovascular diseases, including coronary heart disease, congestive heart failure, valvular calcifications, strokes, and hypertension.

There was noted significant importance of vitamin D deficiency [25 (OH) D <20 ng/мл]. In addition to its clearly defined role in the metabolism of bones and calcium, vitamin D has been identified as an important factor in the pathogenesis of cardiovascular diseases. Deficiency of vitamin D has many adverse effects, contributing to endothelial dysfunction, proliferation and migration of smooth muscle cells, calcification of the arteries walls [5].

In addition, vitamin D deficiency has an adverse effect on systemic conditions that contribute to atherosclerosis development, such as insulin resistance,  $\beta$ -cells dysfunction, dyslipidemia. Thus, it can be argued that vitamin D deficiency, acting directly or indirectly, has many effects on the function and pathology of cells and tissues involved in the atherogenic process [11].

## The purpose

The purpose – to study the effect of hyperhomocysteinemia and vitamin D deficiency on IHD course in patients with multifocal atherosclerosis and in cases of coronary arteries primary lesion.

## Materials and methods

The study was performed at the Department of Hospital Surgery of Zaporozhye Medical University in the Department of Cardiovascular Surgery. The study included the results of patients suffering from ischemic heart disease and multifocal atherosclerosis examination after informed consent obtainment. Criteria for inclusion in the study were patients with coronary heart disease with coronary and carotid arteries confirmed pathology.

Patients over 70 years of age, patients with oncological pathology, valvular heart diseases, kidney diseases, rheumatic diseases, patients with diseases of the gastrointestinal tract were not included in the study.

Data from 58 patients were analyzed. There were 55 male and 3 female patients. The average age of patients was  $58.2 \pm 5.48$  years.

The groups did not significantly differ in sex, age, complications and comorbidities.

The definition of stable angina functional class was performed by the Canadian Association of Cardiologists. Unstable angina pectoris (UA) was diagnosed according to the criteria of the New York Association of Cardiologists. The UA classes were determined according to E. Braunwald (1994).

93.1 % of patients had stage III hypertensive disease.

The majority of patients were overweight, the average BMI was  $29.6 \pm 3.10$ . 35 patients suffered from myocardial infarction (56.3 %).

According to the classification of Canadian Cardiovascular Society angina (CCSA), there were 23 (36.9 %) patients with angina pectoris of IV functional class (FC), angina pectoris of III FC – 20 (34.4 %). Unstable angina was detected in 15 (25.8 %) patients. Stage I heart failure (HF) was detected in 33 (56.8 %) patients, stage II HF was detected in 25 (43.1 %) patients.

All patients were divided into 2 groups based on the prevalence of atherosclerosis. The 1st group consisted of 33 patients with multifocal atherosclerotic lesion (coronary and carotid arteries): 30 (90.9 %) men, 3 (9.09 %) women, average age was 59 (56–64) years. The second group included patients with isolated coronary arteries (CA) lesion: 25 (100 %) men, mean age was 59 (50–63) years (Table 1).

Examination of patients included, in addition to general clinical (patient complaints, anamnesis, examination, palpation, percussion, auscultation), laboratory (general blood test, glucose, creatinine and urea blood levels), instrumental examinations: radiography of chest organs, fibrogastroduodenoscopy and ultrasound examination of the abdominal cavity organs.

The level of homocysteine and vitamin D in plasma was studied using the «Sun rise TS» immunoenzyme analyzer, «AiA 2000ST» immunofluorescence analyzer manufactured by «Tosoh Bioscience» Japan, electrochemiluminescence analyzer «Cobas E 411» manufactured by Roche Diagnostics, Germany.

**Table 1.** Characteristics of the examined patients

Indexes	Group 1 (n = 33)	Group 2 (n = 25)
Hypertensive disease	33 (100 %)	25 (100 %)
Postinfarction atherosclerosis	23 (69.6 %)	12 (48 %)
Diabetes	6 (18.1 %)	4 (16 %)
Average BMI	$29.1 \pm 3.10$ кг/м <sup>2</sup>	$30.5 \pm 2.92$ кг/м <sup>2</sup>
Angina pectoris IV FC	17 (51.5 %)	6 (24 %)
Angina pectoris III FC	9 (27.2 %)	11 (44 %)
Unstable angina	7 (21.2 %)	8 (32 %)
Stage I heart failure	18 (54.5 %)	15 (60 %)
Stage II heart failure	15 (45.4 %)	10 (40 %)

Coronary angiography was performed on the Toshiba Medical Systems Corporation, INFX-8000V Infinix VF-i/SP angiographic system, and Toshiba diagnostic tomograph «TSX-101 A» (Japan). The carotid arteries were examined with the help of diagnostic tomographs Asteion S4 Toshiba and TSX-101 A Toshiba (Japan), ultrasound diagnostic dopplerographic devices: Philips En Visor HD and Toshiba Xario.

Most of the data was processed by nonparametric methods using the statistical software package «Excel», Statistica 6.0. Statistical analysis of the study results was carried out using a computer program for statistical data processing: in the form of mean values ( $M \pm m$ ), nonparametric in the form of  $Me$  (25–75 %). To assess the differences significance in the quantitative parameters between two independent samples, the Mann-Whitney test was used. The reliability of differences in the groups was accepted at a level of statistical significance  $P < 0.05$ .

## Results and discussion

According to the results of selective coronary angiography, 56 (96.5 %) patients had multivessel lesions of the coronary arteries, both in the right and left coronary arteries basin and in 2 (3.44 %) patients there was isolated lesion of one coronary artery.

In group 1–3 and 4 vascular lesions of the coronary arteries predominated (81.8 %). and in the second group – 2 vascular lesions of the CA were predominant, which was 36 %.

In the first group, lesions of brachiocephalic arteries by angiography of the aortic arch branches and duplex scanning of the cerebral arteries were detected in 33 patients (100 %). The most common lesion was internal carotid artery (ICA), mainly from both sides, which amounted to 56.8 % (33 patients). In the second group brachiocephalic arteries lesion was not revealed.

In 93.1 % of cases, patients underwent direct myocardial revascularization, and 4 (6.89 %) patients were implanted with drug-eluting stents in coronary arteries. In the first group 9 patients (27.2 %) underwent simultaneous surgical intervention in the volume: direct myocardial revascularization and carotid endarterectomy (internal carotid artery).

About half (45 %) of the examined patients had an elevated homocysteine level in the blood plasma of more than  $15 \mu\text{mol/l}$ . In the first group of patients (multifocal atherosclerosis), homocysteine concentration was  $19.5$  ( $14$ – $28.7$ )  $\mu\text{mol/l}$ . This index was significantly higher

**Table 2.** Analysis of age, concentration of HC, vitamin D and cholesterol in the study groups

	Group 1	Group 2	P
Age (years)	59 (56–64)	59 (50–63)	0.158
Homocysteine ( $\mu\text{mol/l}$ )	19.5 (11.43–45.41)	16.62 (11.19–29.24)	0.009
Vitamin D (ng/ml)	18.84 (14.27–27.62)	23.78 (19.41–40.08)	0.008
Cholesterol (mmol/l)	4.40 (3.56–5.59)	4.62 (4.09–6.16)	0.132

The average result is presented by Me (25–75 %), P: U Mann–Whitney criterion.

(Table 2) than in the patients of the 2nd group, which was 16.62 (11.19–29.24)  $\mu\text{mol/l}$ .

At the same time 51.7 % of patients had a slight degree of severity (15–30  $\mu\text{mol/L}$ ), and 17.2 % had an average degree of hyperhomocysteinemia (30–100  $\mu\text{mol/l}$ ). A severe degree (more than 100  $\mu\text{mol/l}$ ) was not detected.

There was also a decrease in vitamin D levels in patients of both groups. In the first group vitamin D level was 18.84 (14.27–27.62) ng/ml, and in the second group – 23.78 (19.41–40.08) ng/ml.

These values confirmed the presence of vitamin D deficiency both in patients with advanced atherosclerosis and in individuals with isolated coronary pathology.

The level of total cholesterol was within the normative values and in the first group was 4.40 (3.56–5.59) mmol/l, and in the second – 4.62 (4.09–6.16) mmol/l. The obtained value of U ( $P < 0.132$ ) was in the zone of insignificance. As a result of the analysis, there was no correlation between lipidogram indices, plasma homocysteine level and prevalence of atherosclerosis.

Of practical interest is the analysis of blood plasma homocysteine concentration values, depending on the degree and area of atherosclerotic lesion. In our study, in patients with multifocal sclerosis (group 1), the mean plasma homocysteine concentration was significantly higher and reached 19.5  $\mu\text{mol/l}$ , and in the 2 group patients (isolated CA lesions) a total level was 16.62  $\mu\text{mol/l}$ .

Patients of the 1st group with multifocal atherosclerosis had significantly higher homocysteine indices and a more pronounced vitamin D deficiency. At the same time, vitamin D deficiency was detected in patients of both groups (Table 2).

We have found a clear relationship between the level of homocysteine and the prevalence of atherosclerotic lesions. These results indicate a possible destabilization of atherosclerosis course with hyperhomocysteinemia in combination with vitamin D deficiency.

Patients of the 1st group with multifocal atherosclerosis had significantly higher homocysteine indices and a more pronounced vitamin D deficiency. At the same time, vitamin D deficiency was detected in patients of both groups.

Consequently, there is a double adverse effect on the course of IHD and the results of myocardial revascularization, which should be taken into account in drug therapy after surgical interventions.

## Conclusions

1. Hyperhomocysteinemia, vitamin D deficiency – are the risk factors for coronary heart disease development and are associated with an unfavourable course of coronary pathology.

2. All patients with ischemic heart disease had vitamin D deficiency and hyperhomocysteinemia, more pronounced with multifocal atherosclerosis, which should be considered when prescribing medication after myocardial revascularization and interventions on the carotid arteries.

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