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The evaluation of the coronary arteries calcification degree by the method of cardiovascular MSCT in patients with vitamin D and homocysteine metabolism disturbance

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

In spite of diagnostics and treatment methods development, the ischemic heart disease (IHD) is still the leading cause of disabilities and mortality level in the population. The main reason for IHD pathogenesis is endothelial vascular dysfunction, which further initiates the atherogenesis. The revealing of hyperhomocysteinemia and vitamin D deficiency is determined to increase the risk of the early coronary arteries (CA) atherosclerosis and thrombosis development and to be the prognostic marker of a lethal case. Traditionally, the selective coronary angiography is used to obtain an image of the CAs. However, with the advent of multispiral computed tomography (MSCT), the technique of CT angiography of coronary vessels was introduced, which today has opened wide prospects for determining the degree of coronary calcification and non-invasive evaluation of the anatomy and the degree of CAs narrowing.

The aim of the research is to evaluate the degree of CA calcification by the MSCT method in patients with hyperhomocysteinemia and vitamin D deficiency and to determine the correlation between these parameters.

Materials and methods. The data of 39 patients who were diagnosed with the CAs pathology by MSCT CAG were analyzed.

Results. Patients with high calcium index, greater than 400, with an average cholesterol level of 20.69 ± 2.10 mmol/l, had significantly higher plasma cholesterol levels ($P < 0.022$ by Mann–Whitney criteria) compared to patients with calcium index less than 400 (mean homocysteine was 13.51 ± 0.97 mmol/l), and greater area of CAs lesions.

Conclusions. The MSCT CAG can be used as a screening method to diagnose and clarify the nature of CA lesion. Due to the proven correlation between CI and homocysteine levels, the careful treatment of hyperhomocysteinemia is required both before and after CA surgery.

Key words: homocysteine, vitamin D, hyperhomocysteinemia, multispiral computed tomography, coronary calcium index.

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Оцінювання ступеня кальцинозу коронарних артерій методом МСКТ серця в пацієнтів із порушенням метаболізму вітаміну D і гомоцистеїну

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Незважаючи на розвиток діагностики та методів лікування, ішемічна хвороба серця (ІХС) залишається провідною причиною інвалідизації та смертності населення. Основна причина ІХС – ендотеліальна судинна дисфункція, що ініціює атерогенез. Показано, що наявність гіпергомоцистеїнемії та дефіциту вітаміну D підвищує ризик раннього розвитку атеросклерозу та тромбозу коронарних артерій і є прогностичним маркером летального наслідку. Традиційно для отримання зображення коронарних артерій використовують селективну коронарну ангіографію. Однак із появою мультиспіральної комп'ютерної томографії (МСКТ) уведена методика КТ-ангіографії коронарних судин, що нині відкрила широкі перспективи визначення ступеня коронарної кальцифікації та неінвазивного оцінювання анатомії та ступеня звуження коронарних артерій.

Мета роботи – оцінити ступінь кальцифікації коронарних артерій методом МСКТ у пацієнтів із гіпергомоцистеїнемією та дефіцитом вітаміну D і визначити кореляцію цих параметрів.

Матеріали та методи. Вивчили дані 39 пацієнтів, яким діагностували патологію коронарних артерій методом МСКТ КАГ.

Результати. Пацієнти з високим кальцієвим індексом (понад 400) і середнім рівнем гомоцистеїну 20,69 ± 2,10 ммоль/л мали вищий рівень гомоцистеїну у плазмі крові ($p < 0,022$ за критерієм Манна–Уітні) порівняно з пацієнтами з кальцієвим індексом менше ніж 400 (середній показник гомоцистеїну становив 13,51 ± 0,97 ммоль/л) та більшу кількість уражень коронарних артерій.

Висновки. МСКТ КАГ можна використовувати як скринінг для діагностики та уточнення характеру ураження коронарних артерій. Зважаючи на доведену кореляцію між рівнями кальцієвого індексу та гомоцистеїну, необхідне ретельне лікування гіпергомоцистеїнемії до і після операції на коронарних артеріях.

Ключові слова: гомоцистеїн, вітамін D, гіпергомоцистеїнемія, мультиспіральна комп'ютерна томографія, коронарний індекс кальцію.

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Оценка степени кальциноза коронарных артерий методом МСКТ сердца у пациентов с нарушением метаболизма витамина D и гомоцистеина

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Несмотря на разработку методов диагностики и лечения, ишемическая болезнь сердца (ИБС) по-прежнему является основной причиной инвалидности и причиной смертности населения. Основная причина развития патогенеза ИБС – эн-

Ключевые слова: гомоцистеин, витамин D, гипергомоцистеинемия, мультиспиральная компьютерная томография, коронарный кальциевый индекс.

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дотелиальная сосудистая дисфункция, которая в инициирует атерогенез. Наличие гипергомоцистеинемии и дефицита витамина D определенно увеличивает риск развития атеросклероза и тромбоза коронарных артерий (КА) и является прогностическим маркером летального исхода. Традиционно селективная коронарная ангиография используется для получения изображения коронарных артерий. Однако с появлением мультиспиральной компьютерной томографии (МСКТ) была введена методика КТ-ангиографии коронарных сосудов, которая открыла широкие перспективы для определения степени коронарной кальцификации и неинвазивной оценки анатомии и степени сужения коронарных артерий.

Цель работы – оценить степень кальцификации коронарных артерий методом МСКТ у пациентов с гипергомоцистеинемией и дефицитом витамина D и определить корреляцию этих параметров.

Материалы и методы. Изучены данные 39 пациентов, которым диагностирована патология коронарных артерий методом МСКТ КАГ.

Результаты. Пациенты с высоким кальциевым индексом (более 400) и средним уровнем гомоцистеина 20,69 ± 2,10 ммоль/л имели значительно более высокие уровни гомоцистеина в плазме ($p < 0,022$ по критерию Манна–Уитни) по сравнению с пациентами с кальциевым индексом менее 400 (средний показатель гомоцистеина – 13,51 ± 0,97 ммоль/л) и большее количество поражений коронарных артерий.

Выводы. МСКТ КАГ можно использовать в качестве скрининга для диагностики и уточнения характера поражений коронарных артерий. Благодаря доказанной корреляции между уровнями кальциевого индекса и гомоцистеина необходимо тщательное лечение гипергомоцистеинемии до и после операции на коронарных артериях.

At present, there is a great deal of interest in new diagnostic techniques capable of determining the severity of coronary arteries (CA) atherosclerosis, and of identifying patients with high risk for coronary diseases cases. The alternative cardiovascular risk (CVR) determination methods are supposed to use the non-invasive imaging techniques [2,3].

The MSCT CAG is widely used in the world for the initial diagnostics of the atherosclerosis according to the quantitative assessment of the coronary arteries calcification degree based on X-ray absorption and area of calcinosis coefficient, which is expressed in relative units of calcium index (CI), being proposed by A. Agatston in early 1990. The quantitative assessment of CA calcinosis with the CT is useful for monitoring the progression of CA atherosclerosis and for evaluating the effectiveness of its treatment. In patients with already diagnosed IHD, the MSCT helps to determine the dissemination and location of the CAs. The density factor is calculated by the peak density of the calcification zone, which is expressed in Hounsfield units (HU). The coronary artery calcinosis (CAC) is defined as an area with a density greater than 130 HU [7–10].

The MSCT usage significantly shortens the examination time. An advantage of the MSCT is the low signal-to-noise ratio, which allows reliable detection of minor calcinosis even in patients with obesity. Such techniques provide opportunities for synchronization of ECG results with quantitative calculation of calcinosis [1,4].

The contraindications to the CA MSCT examination are the presence of atrial fibrillation, extrasystole, hypothyroidism, terminal renal dysfunction, contrast media hypersensitivity [6,7].

The interpretation of the coronary calcium index (CCI) (A. Agatston) data:

0 – no atherosclerotic plaque (AP), the probability of IHD is very low, cardiovascular risk is very low.

1–10 – minimum AP, IHD is unlikely, cardiovascular risk is low.

1–100 – low AP, possible minimal or moderate stenosis, cardiovascular risk is moderate.

101–400 – moderate AP, high probability of IHD, cardiovascular risk is moderate-to-high.

>400 – severe atherosclerosis, high probability of significant stenosis, cardiovascular risk is high.

According to the meta-analysis of the prospective studies (n = 17593), the calcium index is an independent risk factor for the cardiovascular diseases development [9].

Currently, the determination of the calcification degree of the CAs and the data obtained regarding the interpretation of the results are still under discussion. Patients with very high calcium index (>1000) have been proved to have a 25 % higher risk of myocardial infarction or coronary death per year [3,5].

Some studies show that the hyperhomocysteinemia is an important and independent modifiable risk factor for cardiovascular diseases [11]. It is also the risk factor for atherothrombotic complications in the general population. An increased concentration of homocysteine in the blood serum has toxic effects on the endothelial cells, that further potentiates low-density lipoprotein (LDL) oxidation and promotes "proinflammatory" high-density lipoproteins (HDL) formation [11,12]. The severity of hyperhomocysteinemia correlates with the risk of death within the first 5 years since a cardiovascular disease was diagnosed [14]. The significant relationship between the homocysteine level and mortality in patients with angiographically confirmed CA diseases has been revealed [13].

The recent results have shown that vitamin D deficiency (VDD) promotes the development of various cardiometabolic conditions such as hypertension, diabetes mellitus and CA diseases [16].

Danish researchers led by Dr. Peter Brondum-Jacobsen (Copenhagen University Hospital, Denmark), published an article pointing to a close link between low vitamin D levels and increased incidences of IHD, myocardial infarction (MI) and early death [15].

Aim

The aim of the research is to evaluate the degree of CA calcification by the MSCT method in patients with hyperhomocysteinemia and vitamin D deficiency and to determine the correlation between these parameters.

Materials and methods

The study was performed at the Department of Hospital Surgery of Zaporizhzhia State Medical University in

the Cardiac Surgery unit. The article analyzes the data of 39 patients, who underwent MSCT of the CAs calculating the calcification index and determining homocysteine and vitamin D levels from September 2018 to May 2019. There were 33 men (84.6 %) and 6 women (15.4 %). The age of the patients was 61.9 ± 1.33 years old (*Table 1*).

Most patients were overweight – BMI was 28.37 ± 3.82. Myocardial infarction was in 25 patients (64.1 %). Angina pectoris class IV was detected in 7 (17.94 %) patients, angina class III was in 30 (76.9 %) patients. Unstable angina was only in 2 patients (5.12 %). Stage I heart failure was in 2 (5.12 %) patients, stage II was in 37 (94.8 %) patients.

The average homocysteine concentration was 17.93 ± 1.44 mcmol/l, vitamin D 44.5 ± 2.92 ng/ml, and cholesterol – 4.75 ± 0.21 mmol/l. Concerning the concomitant pathology, the presence of internal carotid artery stenosis in 30 (76.9 %) patients and obliterating atherosclerosis of the lower extremities arteries in 32 (82.05 %) patients should be noted. The disease duration was 21.5 ± 2.8 months from the first symptoms onset.

The patients were divided into two groups, depending on the calcium index level. The first group included 15 patients with moderate-to-high cardiovascular risk (calcium index up to 400) and an average age of 57.4 years old. The second group consisted of 24 patients with high RSR (calcium index greater than 400) and an average age of 64.5 years old.

The examination of the patients included: general clinical stage (complaints, anamnesis, physical), laboratory studies (general blood test, glycosylated hemoglobin, glucose, creatinine, blood urea), instrumental examinations: chest X-ray, FGDS, abdominal ultrasound.

The plasma homocysteine and vitamin D levels were measured using a "Sunrise TS" immunoassay analyzer, AIA 2000ST immunofluorescence analyzer made in "Tosoh Bioscience", Japan, "Cobas e 411" electrochemiluminescent analyzer, made in "Roche Diagnostics", Germany. The carotid artery examination was performed using Toshiba (Japan) "TSX-101A" and Toshiba (Japan) "Asteion S4" diagnostic tomographs, the ultrasound diagnostic Dopplers: Philips Envisor HD and Toshiba Xario.

The MSCT of the heart was performed on a 64-section spiral CT scanner "Aquilion TSX-101A" Toshiba (Japan). The study was performed in a schedule after a therapy assigning for reducing heart rate up to 60 beats per minute. Intravenously, through the vein of the upper extremity, a patient was administered 100 ml of contrast medium (Ultravist 370, Bayer, Germany) followed by a "flash" in the form of 50 ml of saline. Injection rate was 5 ml/sec. The resulting images were processed on an AW Discovery workstation with Volume Share 5 software.

Most of the data were processed by non-parametric methods using the statistical package "Excel", Statistica 6.0. Statistical analysis of the study results was performed using a computer program of statistical data processing and presented as averages (M ± m), non-parametric – in the form of Me (25 % –75 %). The Mann–Whitney test and the Spearman coefficient were used to assess the significance of differences in quantitative parameters between two independent samples. The significance of differences between groups was assumed at the level of statistical significance $P < 0.05$.

Table 1. Characteristics of the patients (n = 39)

Hypertension	n = 37 (94.8 %)
Tobacco smoking	n =12 (30.7 %)
Hyperlipidemia	n =9 (23.07 %)
Hyperhomocysteinemia	n = 35 (89.7 %)
Vitamin D deficiency	n = 10 (25.6 %)
Diabetes mellitus	n = 7 (17.9 %)
Postinfarction cardiosclerosis	n = 25 (64.1 %)
AF LV	53.02 ± 1.14 %

Table 2. Results of MSCT CAG (n = 39)

			Abs. number of stenoses	CCI	Calcium volume
RCA	Proximal RCA		24	262.84	213.87
	Mid RCA		20		
	Distal RCA		8		
LCA	Left main		11	89.58	70.71
	LAD	Proximal	31	375.30	306.07
		Mid	13		
		Distal	1		
	Diagonal 1		15		
	Diagonal 2		5		
	LCx		26	209.23	179.87
	OMB 1 (obtuse marginal branch)		10		
	OMB 2		3		

Results

During the examination of patients who underwent echocardiography, Holter ECG monitoring and dosed exercise testing, 39 patients with severe symptoms of IHD were selected. These patients were tested for homocysteine, vitamin D, glycosylated hemoglobin. In patients with clear signs of coronary heart disease and hyperhomocysteinemia, a non-invasive study of CA – MSCT CAG was performed. The CA lesion was then confirmed. We were interested in the association between calcium index and both homocysteine and vitamin D levels as a possible screening for IHD.

According to the MSCT results, 37 patients were diagnosed with multiple vascular lesions of the CAs (*Table 2*), both the right and left CAs. The total number of affected CAs was 139. One case was diagnosed with the only right CA (RCA) lesion, therefore the stenting of the RCA was performed. A patient with bilateral CA (left anterior descending artery and left circumflex artery) was implanted with 2 stents in the left anterior descending artery and circumflex artery.

The most commonly reported lesions were proximal segments of left anterior descending artery (LAD) (n = 31) and circumflex artery (LCx) (n = 26).

Based on the MSCT CAG data, the indications for direct myocardial revascularization were present in 37 patients.

A total of 127 distal anastomoses were performed, with an average of 2.5 ± 1.0 (1–4) anastomoses per patient. In nine cases, it was not possible to perform a distal anastomosis because of diffuse lesions along the entire length of the arteries and the small caliber of the latter. Thus, the specificity of the method according to our study was 93.5 %.

In 8 patients, the significant concomitant pathology was detected, the correction of which could be performed in combination with coronary artery bypass grafting.

Table 3. Type and number of simultaneous operations (n = 8)

CABG + Aortic valve replacement	50.0 % (n = 4)
CABG + Carotid endarterectomy	37.5 % (n = 3)
CABG + sigmoid colon resection – colostomy	12.5 % (n = 1)

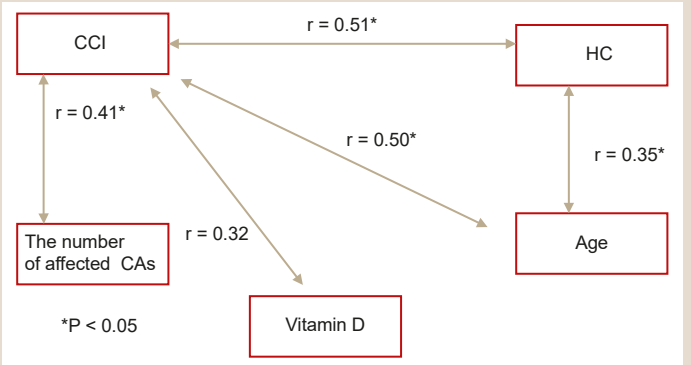

Fig. 1. Scheme of correlation between CCI and risk factors.

Therefore, it was decided to carry out a simultaneous intervention. A total of 8 (20.5 %) similar interventions were performed (*Table 3*).

The average duration of a surgery in simultaneous operations was 295.8 ± 66.9 minutes. In combined heart valves prosthetics and coronary artery bypass grafting (CABG), the latter CABG was performed first, and the next stage was the prosthetics. The carotid endarterectomy was performed in the first stage, simultaneously with the venous shunts removal.

In the long term, 20.3 ± 1.4 months, the mortality rate was 5.12 %. One patient died of acute MI in the early post-operative period. The second patient died a month after the surgery due to large intestinal bleeding. During this period, all the patients took aspirin, clopidogrel and statins. In the cases of cardiac valve prostheses, the indirect anticoagulants were taken too.

We found an increase in CI in IHD patients with higher levels of blood plasma homocysteine, compared with the individuals having mild hyperhomocysteinemia. Besides, the correlation of increased calcium deposition in the CA walls was found with age (r = 0.35), homocysteine level (r = 0.51) and the number of affected CA (r = 0.50). No significant association between CI and vitamin D level was detected (r = 0.04) (*Fig. 1*).

The patients with high CI, more than 400, who were in the second study group with an average homocysteine level of 20.69 ± 2.10 mmol/l, had significantly higher homocysteine plasma levels (P < 0.022 by the Mann–Whitney criteria), compared with the patients in the first group (an average homocysteine was 13.51 ± 0.97 mmol/l) and a larger area of the CA lesions. These data should be considered in the early diagnosis of IHD.

Discussion

Thus, we found out that the higher homocysteine level is, the higher the CI and the number of affected CAs. These data suggest the association between HHC and the coronary calcium in patients with IHD. Patients with normal homocysteine levels had less pronounced coronary arteries calcinosis and the number of affected CAs.

Besides, we managed to reveal the correlation between glycated hemoglobin (HbA1c) and both homocysteine (r = 0.38) and vitamin D levels (r = 0.32), which may indicate the direct involvement of carbohydrate metabolism disorders in patients with impaired homocysteine and vitamin D metabolism and more pronounced atherosclerosis.

Hence, the homocysteine level and patient age are the predictors of CAC.

According to our data, the frequency of detection and the severity of coronary calcification according to MSCT of the CAs at the revealed HHC with increasing age were much higher than in the individuals with normal blood plasma homocysteine.

In the examination of men and women aged 40–65 years without established cardiovascular disease in order to detect the early signs of coronary atherosclerosis it is necessary to measure the level of homocysteine as an early initial test in the absence of established diagnosis of IHD with atypical chest pain. In the second stage, the coronary calcification screening by MSCT of CAs in an outpatient setting to confirm CAC in assessing the level of IHD complications risk.

In a recently published study, T. S. Polonsky (5878 patients from the MESA study (Multi-Ethnic Study of Atherosclerosis) were observed for an average of 5.8 years) showed additional benefits of adding the CCI to common risk factors – age, gender, smoking, systolic blood pressure, total cholesterol and lipoprotein cholesterol low density, race/nationality. The addition of CCI increased the area under the coronary event prediction curve from 0.76 to 0.81; 26 % of subjects were reclassified when CCI was added to the standard risk factors [17].

Lamont D. H. et al. examined 153 patients who were tested for coronary calcium by MSCT CAG: 27 % of subjects had a false-positive test result, while the sensitivity of the sample in the detection of calcium in the arteries was 98 %. The researchers concluded that measuring coronary calcium with MSCT CAG may help identify patients with false-positive stress tests [18].

Another study showed that patients with a low CCI score may still have coronary artery disease, although rarely enough, and in such cases, the aortic valve calcification presence can help identify patients with coronary heart disease [19].

Berman D. S. et al. found a correlation between an increase in CCI and the presence of an ischemic response when scanning perfusion using SPECT in 1195 patients without clinical signs of coronary heart disease. N. D. Wong et al. showed that the presence of metabolic disorders (metabolic syndrome or diabetes mellitus) reduces the threshold in CCI level at which the frequency of myocardial ischemia detection increases to 100 compared with 400 in patients without such abnormalities [20].

Recent studies confirmed the relationship between the CI and risk factors for atherosclerosis, which requires a more detailed study on this problem.

However, the effects of homocysteine and vitamin D deficiency on the artery vascular wall, the CA calcification degree, and the effect of medication are not sufficiently addressed in medical publications.

After analyzing the data of the world literature, we came to the conclusion that today, the problems of timely diagnosis of coronary heart disease in patients with impaired vitamin D and homocysteine metabolism and the solution to the issue of drug treatment before and after surgery are not completely resolved in this direction.

Conclusions

1. In addition to the standard methods, the patients with suspected the ischemic heart disease are advised to examine the metabolism of homocysteine, vitamin D, and glycated hemoglobin.

2. Ischemic heart disease patients with hyperhomocysteinemia are characterized by the increase in total calcium index, which indicates the development of early coronary artery calcification.

3. The MSCT CAG can be used as a screening method to diagnose and clarify the nature of the coronary arteries lesion.

4. Due to the proven correlation between calcium index and homocysteine levels, the careful treatment of hyperhomocysteinemia is required both before and after surgery for coronary, carotid and other arteries.

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