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MULTIFOCAL ATHEROSCLEROSIS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS COMBINATION WITH METABOLIC SYNDROME

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The purpose of the study was to assess of the frequency of multifocal atherosclerosis and plural atherosclerotic plaques in the different vessels of patients with type 2 diabetes mellitus and its combination with metabolic syndrome. Results showed that 12.02 % of patients with diabetes mellitus without metabolic syndrome had multifocal atherosclerosis with simultaneous damage of 2 vessels, in patients with diabetes mellitus+metabolic syndrome – 22.75 % ($p<0.001$). Significantly more frequent cases of multifocal atherosclerosis with simultaneous involvement of several vascular beds in patients with diabetes mellitus without metabolic syndrome and with diabetes mellitus+metabolic syndrome in contrast to patients without diabetes and metabolic syndrome ($p<0.01$). Thus, a significant effect of diabetes mellitus on the rapid development and progression of atherosclerosis, which is exacerbated with the accession of the metabolic syndrome, has been demonstrated.

Key words: atherosclerotic plaques, type 2 diabetes mellitus, metabolic syndrome, arterial hypertension

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МУЛЬТИФОКАЛЬНИЙ АТЕРОСКЛЕРОЗ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ У ПОЄДНАННІ З МЕТАБОЛІЧНИМ СИНДРОМОМ

Метою дослідження стала оцінка частоти мультифокального атеросклерозу та множинних атеросклеротичних бляшок у різних судинах у хворих на цукровий діабет 2 типу у поєднанні з метаболічним синдромом. Результати показали, що у хворих на цукровий діабет без метаболічного синдрому мультифокальний атеросклероз з одночасним ураженням 2-х судин мав місце у 12,02 % пацієнтів, у хворих з комбінацією цукровий діабет+метаболічний синдром – у 22,75 % ($p<0,001$). Достовірно частіше зустрічалися випадки мультифокального атеросклерозу з одночасним ураженням кількох судинних русел у хворих на цукровий діабет без метаболічного синдрому та з комбінацією цукровий діабет+метаболічний синдром на відміну від хворих без цукрового діабету та метаболічного синдрому ($p<0,01$). Таким чином, показано значний вплив цукрового діабету на швидкий розвиток та прогресування атеросклерозу, що посилюється з приєднанням метаболічного синдрому.

Ключові слова: атеросклеротичні бляшки, цукровий діабет 2 типу, метаболічний синдром, артеріальна гіпертензія.

The problem of multifocal atherosclerosis is currently extremely relevant. Complications of multifocal atherosclerosis, such as coronary heart disease and cerebral stroke, are the leading causes of death and disability in developed countries' populations [1, 5, 13].

It is known that atherosclerotic lesions of the vascular bed often complicate the clinical course of type 2 diabetes mellitus (DM-2) [3, 4]. On the other hand, the pathogenic effect of all components of the metabolic syndrome (MS) (arterial hypertension, hyperglycemia, obesity, lipid metabolism disorders) is also mainly directed to the vascular system [7, 8].

The causes of this process are close related to the pathogenetic mechanisms of these metabolic disorders. Diabetes mellitus comprises a group of carbohydrate metabolism disorders that share a common main feature of chronic hyperglycemia that results from defects of insulin secretion, insulin action, or both. Insulin is an important anabolic hormone, and its deficiency leads to various metabolic abnormalities in proteins, lipids, and carbohydrates. Various glucose metabolism parameters have different effects the degree of arterial stiffness and presence of carotid atherosclerosis. Atherosclerosis develops as a result of a multistep process ultimately leading to cardiovascular disease associated with high morbidity and mortality. Alteration of lipid metabolism is a risk factor and characteristic feature of atherosclerosis [11].

However, the data available so far do not allow for developing effective anti-inflammatory therapeutic and preventive strategies that would stop multifocal atherosclerotic lesion progression or induce lesion reduction [2].

In recent years, to assess the functional and structural changes in the vessels, ultrasonic methods of vascular examination have been increasingly used, which make it possible to visualize intravascular atherosclerotic plaques (AP), which directly indicate the development of an atherosclerotic lesion [10].

The purpose of the study was to provide a comparative examination of the number of detected atherosclerotic plaques in patients with type 2 diabetes mellitus and its combination with metabolic syndrome in comparison with persons without type 2 diabetes mellitus and metabolic syndrome of similar age and sex composition.

Material and methods. 233 patients were examined: 139 (59.7 %) men and 94 (40.3 %) women, aged 27 to 81 years with an average age of 59.72+8.4 years. In 73 patients (49 men and 24 women) isolated DM-2 was diagnosed, in 74 patients (38 men and 36 women) DM-2 in combination with MS (DM-2+MS), 86 patients (52 men and 34 women) made up the comparison group (CG) – without DM-2 and MS.

The diagnosis of DM-2 was established based on the recommendations of the American Diabetes Association (ADA) and the World Health Organization (WHO) [9]; the diagnosis of MS was established according to the WHO criteria in the presence of two additional of three diagnostic factors [12].

In the group of patients with isolated DM-2, 32 (43.84 %) patients had mild DM-2, and 41 (56.16 %) patients had moderate DM-2. In 49 (67.12 %) patients, DM-2 was in the compensation phase, and in 24 (32.88 %) – in the subcompensation phase.

In the group of patients with a combination of DM-2+MS, 28 (37.84 %) patients had mild DM-2, 46 (62.16 %) patients had moderate DM-2. In 31 (41.89 %) patients, DM-2 was in the compensation phase, in 43 (58.11 %) patients it was in the subcompensation phase.

The degree of arterial hypertension (AH) was established in accordance with the recommendations of the European Society of Hypertension and the European Society of Cardiology [15], while the percentage of patients with various degrees of AH in the groups of patients, regardless of the presence of DM-2 and MS, did not differ significantly. All compared groups of patients were comparable in age ($p=0.3$) and sex (according to Fisher's test, $p=0.2$).

Laboratory research methods included the determination of the level of glucose and insulin in the blood on an empty stomach. All patients underwent ultrasound examination of the main arteries of the neck, upper and lower extremities using the apparatus PHILIPS-HD 11 (Germany) according to the standard technique using a linear probe with a frequency of 7.5 MHz.

Statistical processing of the results of the study was carried out using the statistical computer program Statistica 6.0 from StatSoft (USA). When comparing quantitative data, Fisher's test and Spearman's nonparametric rank correlation test ($\chi 2$) was used. Differences were considered statistically significant at $p<0.01$.

Results of the study and their discussion. All patients in 3 compared groups had concomitant diseases: arterial hypertension in 39 (53.42 %) with DM-2, in all 74 with DM-2+MS and in 44 (51.16 %) in CG; ischemic heart diseases – in 38 (52.05 %) with DM-2, in all 46 (62.16 %) with DM-2+MS and in 34 (39.53 %) in CG; angina pectoris – in 28 (38.35 %) with DM-2, in 33 (44.59 %) with DM-2+MS and in 21 (24.42 %) in CG; chronic heart failure II-III functional degree – in 3 (4.11 %) with DM-2, in 8 (10.81 %) with DM-2+MS and in 1 (1.16 %) in CG; postinfarction cardiosclerosis – in 1 (1.37%) with DM-2; in 7 (9.46 %) with DM-2+MS.

In 88 (37.77 %) patients out of the total number of patients examined, multifocal atherosclerosis was noted with simultaneous damage to several vascular beds.

The combined lesions (CL), reflecting the presence of multifocal atherosclerosis, were significantly more often detected in patients with a combination of DM-2+MS, significantly exceeding the same indicator both in the group of patients with DM-2 without MS, and in CG: 53 (22.75 %) versus 28 (12.02 %) and 9 (3.86 %) ($p<0.001$), respectively. In the group of patients with DM-2+MS, the studied parameter was also significantly higher in comparison with DM-2 without MS ($p<0.001$). In the compared groups in men, multifocal atherosclerosis in the compared groups of patients was detected more often, although the differences did not reach significance.

In the examined patients, vascular damage (VD) were represented by the following main combinations: common carotid artery (CCA)+ External carotid artery (ECA) – in 7 (3.0 %) patients in the DM-2 group without MS, in 13 (5.57 %) in the DM-2+MS group, and in 1 (0.43 %) in CG; CCA+ internal carotid artery (ICA) – in 7 (3.0 %) in the DM-2 group without MS, in 9 (3.9 %) in the DM-2+MS group and in 3 (1.29 %) in the CG; CCA+ vertebral artery (VA) – in 4 (1.72 %) patients in the DM-2 group without MS, in 5 (2.1 %) patients in the DM-2+MS group, in 1 (0.43 %) patient in the CG; CCA+ common femoral artery (CFA) – in 4 (1.72 %) in the DM-2 group without MS, in 9 (3.9 %) in the DM-2+MS group and in 2 (0.86 %) in the CG; CFA+ deep femoral artery (DFA) / superficial femoral artery (SFA) – in 4 (1.72 %) in the DM-2 group without MS, in 5 (2.15 %) in the DM-2+MS group, and in 1 (0.43 %) in the CG;CFA+ popliteal artery (PA) – in 3 (1.29 %) patients in the group of patients with DM-2 without MS, in 4 (1.72 %) in the group of patients with DM-2+MS and in 1 (0.43 %) in the CG. VD of 3 or more vascular beds were represented by a combination of CCA+CFA+PA – in 4 (1.72 %) and CCA+CFA+ brachial artery (AA) – in 4 (1.72 %) patients in the DM-2+MS group. In the DM-2 group without MS and in the CG such VD were not detected.

Our data indicate a significant increase in the frequency of detection of combined atherosclerotic changes in the main arteries of various vascular beds in people with DM-2+MS, even in comparison with patients with DM-2 without MS. So, in the group of patients with DM-2 without MS, out of 73 people, 28 (12.02 %) of the total number of patients) had multifocal atherosclerosis with simultaneous damage to 2 vessels, in patients with a combination of DM-2 + MS, such lesions were detected in 53 (22.75 %) of 74 patients, the differences reached statistical significance ($p<0.001$). At the same time, in the group without DM-2+MS, only 9 patients (3.86 % of the total number of patients) had CL, which was a significantly lower value compared to the first two groups ($p<0.001$).

In most cases, during ultrasound examination of blood vessels, we were able to visualize one intravascular AB of various shapes and sizes, however, often more than 1 AB was visualized in the same vessel, the so-called "multiple" AB.

Multiple AB were not detected in the CG, only in the groups of patients with DM-2 without MS and DM-2+MS.

When several AP were found in one large vessel, their number in most cases did not exceed 2–3 relatively small, hemodynamically insignificant AP. In a few patients, however, the number of AP reached 6–7, in particular in the SA in 2 patients. The number of vessels affected multiple plaques in patients of different groups is showed in Table 1

Table 1

The frequency of detection of multiple AP in various main arteries in patients with DM-2 without and with MS

The number of vessels affected multiple plaques		
	DM-2 without MS	DM-2+MS
External carotid artery (ECA)		
right	1 (0.43 %) (A)	0 (0.0 %)
left	1 (0.43 %) (A)	0 (0.0 %)
generally	2 (0.86 %) (A)	0 (0.0 %)
Internal carotid artery (ICA)		
right	1 (0.43 %) (A)	0 (0.0 %)
left	1 (0.43 %) (A)	0 (0.0 %)
generally	2 (0.86 %) (A)	0 (0.0 %)
Vertebral artery (VA)		
right	3 (1.29 %) (B–3)	1 (0.43 %) (B–1)
left	1 (0.43 %) (B–1)	1 (0.43 %) (B–1)
generally	4 (1.72 %) (B–4)	2 (0.86 %) (B–2)
Axillary artery (AA)		
right	1 (0.43 %) (A–1)	0 (0.0 %)
left	0 (0.0 %)	0 (0.0 %)
generally	1 (0.43 %) (A–1)	0 (0.0 %)
Common femoral artery (CFA)		
right	11 (4.72 %) (A–1, B–3)	1 (0.43 %) (B–1)
left	9 (3.86 %) (B–3)	2 (0.86 %) (A–1)
generally	20 (8.58 %) (A–1, B–3, B–3)	3 (1.29 %) (A–1,B–1)
Deep femoral artery (DFA)		
right	3 (1.29 %) (A–1,B–2)	2 (0.86 %) (A–2, B–1)
left	4 (1.72 %) (A–2,B–1,B–4)	2 (0.86 %) (A–1, B–1)
generally	7 (3.0 %) (A–3, B–1, B–6)	4 (1.72 %) (A–3, B–2)
Superficial femoral artery (SFA)		
right	4 (1.72 %) (A–2,B–2)	3 (1.29 %) (A–2,B–1, D–1)
left	2 (0.86 %) (B–2)	3 (1.29 %) (A–1, B–1, D–1)
generally	6 (2.58 %) (A–2, B–4)	6 (2.58 %) (A–3, B–2, D–2)
Popliteal artery (PA)		
right	3 (1.29 %) (B–2, D–1)	5 (2.15 %) (A–2,B–2)
left	4 (1.72 %) (B–1, B–1, E–1)	4 (1.72 %) (A–2, B–3)
generally	7 (3.0 %) (B–3, B–1, D–1, E–1)	9 (3.86 %) (A–4, B–3, B–2)
Posterior tibial artery (PTA)		
right	1 (0.43 %) (A–1)	2 (0.86 %) (A–2)
left	0 (0.0 %)	0 (0.0 %)
generally	1 (0.43 %) (A–1)	2 (0.86 %) (A–2)

Note: Number of AP: A–2; B–3; C–4; G–5; D–6; E–7

In order to assess the effect of elevated blood pressure (BP) on this factor, we divided the total number of examined patients with DM-2 into 2 subgroups with high and normal BP, presenting the data in Table 2.

Table 2

The frequency of detection of multiple AP in various main arteries in patients with DM-2 with normal and elevated blood pressure levels

Diagnosis	DM-2 + AH (n=39)		DM-2 without AH (n=34)	
	NAV	NAP	NAV	NAP
Common femoral artery (CFA)				
right	9 (12.33 %)	30	2 (2.74 %)	4
left	7 (9.59 %)	24	2 (2.74 %)	7
generally	16 (21.92 %)*	54	4 (5.48 %)*	11
Deep femoral artery (DFA)				
right	4 (5.48 %)	11	0 (0.0 %)	0
left	3 (4.11 %)	8	1 (1.37 %)	3
generally	7 (9.59 %)	19	1 (1.37 %)	3
Superficial femoral artery (SFA)				
right	3 (4.11 %)	8	0 (0.0 %)	0
left	2 (2.74 %)	4	1 (1.37 %)	4
generally	5 (6.85 %)	12	1 (1.37 %)	4
Popliteal artery (PA)				
right	4 (5.48 %)	15	0 (0.0 %)	0
left	3 (4.11 %)	11	2 (2.74 %)	5
generally	7 (9.59 %)	26	2 (2.74 %)	5
Posterior tibial artery (PTA)				
right	0 (0.0 %)	0	1 (1.37 %)	2
left	0 (0.0 %)	0	0 (0.0 %)	0
generally	0 (0.0 %)	0	1 (1.37 %)	2
Axillary artery (AA)				
right	1 (1.37 %)	2	0 (0.0 %)	0
left	0 (0.0 %)	0	0 (0.0 %)	0
generally	1 (1.37 %)	2	0 (0.0 %)	0

Notes: NAV – the number of affected vessels; NAP - Number of atherosclerotic plaques; * – significance of differences between patients with DM-2 without and with AH (Fisher's exact test (two-tailed)=0.00783; $p<0.01$).

The number of detected multiple AP was significantly higher in the subgroup with concomitant hypertension, which was confirmed by significant differences in the occurrence of multiple plaques in the CFA and DFA with a relatively more frequent, but not reaching statistical significance, detection in other main arteries of the lower extremities – PA and SFA. Based on the fact that not a single case of detection of multiple AP was noted in the CG, we came to the conclusion that the presence of DM-2 in patients, especially in cases of combination with AH and MS, led to an increase in the frequency of detection of more extensive and rapidly progressive atherosclerotic changes in the walls of the main arteries.

The results of our study showed significant role of DM-2 and MS as a risk factor in the development of atherosclerosis. There are some similar studies with rather resembling data. So, Sumin AN, et al. retrospectively analyzed 2411 hospital forms of patients with ischemic heart disease subjected to coronary artery bypass grafting (CABG), 317 of them had DM. They revealed that among patients with IHD MFA before CABG was found in 46.1 % of patients with DM and 33.1 % of similar sex and age patients without DM. Recommendation of authors are similar with ours, that patients with DM require focused examination for detection of manifestations of MFA and conduct of necessary curative and preventive interventions [6].

The other study was conducted by Gracheva SA, et al. with the purpose to assess the prognostic value of MFA in patients with DM at high risk for myocardial ischemia. The investigation included 148 patients: 25 with type 1 DM, 73 with type 2 DM, and 50 without DM who had undergone coronary angiography. The authors analyzed not only effect of DM, but also influence of other factors such as smoking, creatinine and fibrinogen levels. It may change the results due to multifactorial effect. Besides that, in their work we cannot find the results in the patient with DM in association with MS. But as in our study Gracheva SA, et al. pointed that in the patients with DM, concurrent atherosclerosis of two or more vascular beds is an important factor for the progression of cardiovascular and renal diseases [3].

Despite of in our work we observed only patient with DM2, some investigator noticed that both types of diabetes mellitus can actually induce atherosclerosis development or further accelerate its progression. Elevated glucose level, dyslipidemia, and other metabolic alterations that accompany the disease development are tightly involved in the pathogenesis of atherosclerosis at almost every step of the

atherogenic process [2, 11, 14]. This theory supports our results about mutual reinforcement DM and MS in our patient.

Conclusions

1. There is a significant increase in the frequency of detection of combined atherosclerotic changes in the main arteries of various vascular beds in people with DM-2 + MS, even in comparison with patients with DM-2 without MS. So, in the group of patients with DM-2 without MS, 12.02% of the total number of patients had multifocal atherosclerosis with simultaneous damage to 2 vessels, in patients with a combination of DM-2 + MS, such lesions were detected in 22.75% of patients ($p<0.001$).

2. Significantly more frequent detection of cases of multifocal atherosclerosis with simultaneous involvement of several vascular beds in groups of patients with DM-2 without MS and with a combination of DM-2+MS in contrast to patients without diabetes and metabolic syndrome ($F=0.00783$; $p<0.01$)

Thus, results of our study confirms that the presence of DM-2 plays the role of its own very significant risk factor in the development of atherosclerosis, the influence of which exceeds the influence of many of the traditional risk factors.

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