

AZERBAIJAN REPUBLIC

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**CONDITION OF MAIN VESSELS OF THE ARTERIAL BED
IN DM-2 PATIENTS, FORECASTING OF POSSIBLE
COMPLICATIONS AND METHODS OF THEIR
CORRECTION**

Speciality: 3205.01- Internal Medicine

Field of science: medicine

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ABSTRACT

of the dissertation for the scientific degree
Doctors of Philosophy in Medicine

Baku – 2021

The dissertation was performed at the Department of Therapeutic and Pediatric Propaedeutic of the Azerbaijan Medical University and at the Consultative and Diagnostic Center "Yasham"

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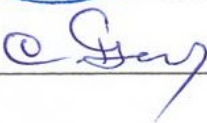
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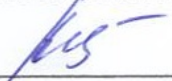
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GENERAL DESCRIPTION OF THE WORK

The relevance of the research: In type 2 diabetes mellitus (DM-2) - one of the most widespread and formidable diseases of our time - a particular place is occupied by damage to the vascular bed due to the rapid onset and progression of the atherosclerotic process. There are numerous indications of an increase in morbidity and mortality among the patients with type 2 diabetes due to cardiovascular, neurological, renal and other complications [Dedov I.I. et al., 2003; Mooradian A.D., 2003].

An arteriosclerotic process in DM-2 is based on a whole cascade of pathogenetic mechanisms, one of the leading links of which is endothelial dysfunction (DE), which is already observed in the early stages of atherosclerosis [Kasatkina SG, Kasatkin SN, 2011; Jude E.B. et al., 2001].

An increase in the level of homocysteine (HL) in the blood is one of the main pathogenetic processes that contribute to a change in the normal structural organization and functional properties of the inner choroid — the intima, in which the endothelial layer of cells is represented [Berestov SA, 2006; Rudnitskaya T.A., 2003].

One of the most informative methods for studying of the internal surface of arteries, which enables indirectly judging the state of their walls, intravascular blood flow and the presence of parietal atherosclerotic lesions, is duplex and triplex ultrasound examination of the great vessels [Schiller NB, Osipov MA, 2005].

Due to the high prevalence of CD-2, research works aimed at studying its cardiovascular complications in comparing the vasomotor and productive functions of the endothelium of the great vessels, the exchange of lipids and HL, as well as the search for adequate methods of pharmacological correction of the revealed disorders, acquire special scientific and practical significance on modern stage.

Purpose of the study:

A comprehensive study of the specifics of violations of the morphological and structural characteristics of arteries and endothelial dysfunction in comparison with the exchange of lipids and HL, cardiovascular complications of patients with type 2 diabetes, as well as the possibilities of optimal pharmacological correction of the revealed violations.

Research Objectives:

1. To study the features of atherosclerotic lesions of the arteries and the primary location of atherosclerotic lesions in patients with and without DM 2

2. To study the functional and structural features and the nature of blood flow through the main vessels of the neck, upper and lower extremities in patients with and without type DM 2.

3. To conduct a comparative assessment of vascular endothelial function disorders using the right brachial artery as an example in patients with and without type DM 2.

4. To study the possibility of predicting the occurrence of vascular complications (myocardial infarction, angina pectoris and others) according to the results of ultrasound examinations, the degree of endothelial dysfunction (ED), lipid and homocysteine metabolic disorders in patients with and without DM 2.

5. To evaluate the possibilities and effectiveness of the pharmacological treatment of DM-2 and its complications, considering the effect on the endothelial function, the state of peripheral blood flow, lipid metabolism and HC.

The main provisions to be defended:

1. Speed parameters of blood flow in the main vessels of the neck, upper and lower extremities in patients with type 2 diabetes have a clear tendency to decrease compared with people of a similar age and gender without type 2;

2. Atherosclerotic changes in the vessels (thickening of the intima-media complex and atherosclerotic plaques) were significantly more often detected in patients with type 2 diabetes;

3. The plasma concentration of HL exceeded normal values, in approximately 75% of patients with type 2 diabetes, while in patients without type 2 diabetes, this indicator was within the normal range, with prevalence in females;

4. The diameter and speed indicators of blood flow in the right brachial artery are significantly higher in patients without type 2 diabetes, and when testing with reactive hyperemia, the degree of increase in the initial diameter and increase in speed indicators of blood flow in the right brachial artery was significantly higher in patients with type 2 diabetes in the absence of gender differences;

5. The frequency of impaired vasomotor and productive functions of the endothelium was significantly higher in patients with type 2 diabetes;

6. In the category of patients (with type 2 diabetes and without type 2 diabetes) with a pathological reaction (narrowing or low increase in diameter and blood flow velocity after a test with reactive hyperemia), significantly higher plasma concentrations of HL and endothelin-1 (Et-1);

7. Adding to the traditional hypoglycemic and hypotensive therapy of tricolor (Tr) or verapamil (VRP) significantly improves the productive and vasomotor function of the endothelium, reduces the level of HC, which follows in parallel with a significant improvement in the clinical condition of patients - a decrease in the number of anginal attacks and ST segment ischemic shifts with Holter ECG monitoring.

Scientific novelty of work

In patients with diabetes mellitus-2, the incidence of atherosclerosis in various vascular pools has been comprehensively studied depending on the state of the peripheral vascular bed, features of peripheral blood flow, degree of DE, lipid and homocysteine metabolism disorders.

The possibilities of optimizing the pharmacological correction of ED and other vascular changes in patients with type 2 diabetes were studied with a dynamic assessment of the

effectiveness of therapy aimed at normalizing the functional properties of the endothelium.

Based on the assessment of the degree of endothelial dysfunction, lipid and HC metabolism, the risk of vascular complications in patients with type 2 diabetes is determined, based on an analysis of a comparison of ultrasound and clinical and laboratory parameters.

The practical significance of the work

The solution of the problems posed in the study will clarify the role of impaired endothelial function of blood vessels, lipid and HL metabolism in changes in peripheral circulation in patients with type 2 diabetes.

The use of ultrasound Doppler studies of the main vascular bed may provide an opportunity for an adequate non-invasive assessment of the functional and morphological characteristics of various vascular pools in patients with type 2 diabetes, taking into account the nature of arterial remodeling and the detection of endothelial dysfunction in the early stages of development of vascular pathology.

Based on the obtained data, a methodology was developed for determining informative ultrasonic parameters (calculation of the TIMC / IAD ratio) characterizing the morphological and functional characteristics of the peripheral, including coronary, vascular bed in patients with type 2 diabetes, contributing, together with the assessment of homocysteine levels in the blood and condition of functional activity of the endothelium, both predicting the risk of developing cardiovascular complications, and constant monitoring of dynamic changes in the process of targeted pharmacological therapies aimed at preventing the cardiovascular complications of DM-2

Implementation of research results The materials of the thesis were introduced into the work of the Department of Therapeutic and Pediatric Propaedeutic of the Azerbaijan Medical University and in the consultative and diagnostic center "Yasham", laid the foundation for the lecture course conducted at the department,

which helped to improve the quality of medical, diagnostic and pedagogical processes.

Testing of the work:

The main provisions of the thesis were reported at the final scientific-practical conference of Azerbaijan. Medical University (2015), at the final scientific-practical conference of Azerbaijan. Medical University (2017), Baku.

The structure and volume of the dissertation:

The dissertation is presented on 200 pages and consists of introduction, literature review, presentation of research methods and material characteristics, two chapters of our own research, discussion of the results, conclusions and practical recommendations. The work is illustrated by tables and figures. The bibliographic index includes the source, 19- table, 32-figure, and 1-diagram. The list of references includes (6- Azerbaijani authors, 135 - authors of the CIS and foreign sources). Publications

Material and research methods

To solve the goal set in the study, a comprehensive examination of 159 patients was carried out: 101 (63.52%) men and 58 (36.4%) women, aged 27 to 81 years with an average age of 59.72 + 8.4 years. All examined were divided into 2 groups depending on the presence of type 2 diabetes (DM-2): group 1-73 patients (49 men and 24 women) with type 2 diabetes; Group 2 (as a comparison group (HS)) - 86 patients (52 men and 34 women) without type 2 diabetes.

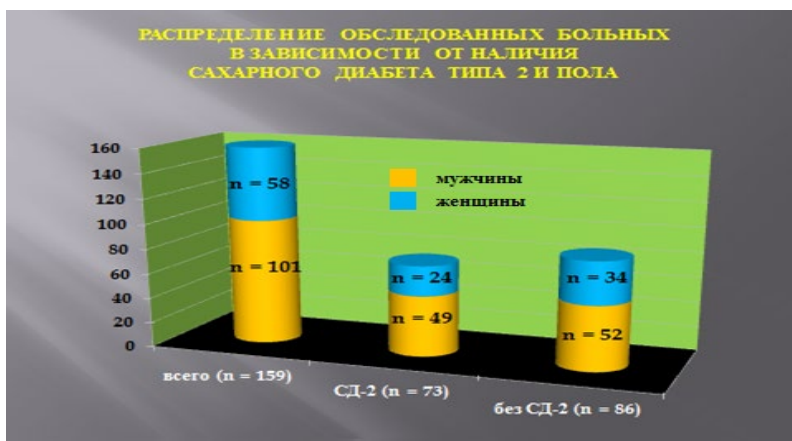
All examined underwent outpatient examination and treatment at the Department of Therapeutic and Pediatric Propaedeutic of the Azerbaijan Medical University and at the Yasham Consultative and Diagnostic Center. During the clinical and instrumental laboratory examination of patients included in this study, information on age and gender was collected and analyzed. The duration of diabetes-2 disease and the degree of diabetes compensation in terms of glycated hemoglobin (glyc. Heme) were

also taken into account. Diagnosis of DM-2 was carried out on the basis of WHO criteria [WHO, 2006].

Of the 73 patients with diabetes mellitus examined by us, 32 (20.12%) had a mild course of diabetes, and 41 (25.79%) patients had moderate diabetes. In 49 (30.82%) patients, DM-2 was in the compensation phase (glyc. Heme. <7%), in 24 (15.09%) - in the sub compensation phase (glyc. Heme. <7.5%).

An objective study took into account the magnitude of heart rate, the presence of arterial hypertension (AH), blood pressure (BP), and the Quetelet index (body mass index, BMI) to exclude the concomitant metabolic syndrome [Gusarova MN, 2000] (Figure 1).

Distribution of examined patients depending on the gender and presence of diabetes mellitus 2



total-(n=159) with diabetes-2 (n=73) without diabetes-2(n=76)

Fig. 1. The number of patients in the compared groups of patients with and without diabetes-2

In a laboratory examination to diagnose and monitor the clinical course of the disease, in addition to the general analysis of blood and urine, the following were studied: fasting blood glucose the level of glycosylated hemoglobin (HvA1C), lipid spectrum

with the calculation of the atherogenic coefficient (AC), the level of homocysteinemia, level Et-1

The complex examination included ultrasound examination of large – caliber arteries.

In order to evaluate the vasomotor function of the endothelium, the standard technique proposed by D. Celermajer, 15 and 60 seconds after cessation of occlusion with a linear 5-15 MHz sensor.

Since in most patients with diabetes mellitus type 2, coronary heart disease is asymptomatic (no anginal attacks) for an objective assessment of myocardial ischemia, patients with type 2 diabetes have undergone constant (for 7 days) Holter monitoring of ECG with registration in standard leads (V3, V5 and AVF) according to the previously described method. In the final assessment of changes ST focused on the main criteria for the detection of myocardial ischemia, used in practice, previously proposed.

Statistical processing of the research results was carried out using the statistical computer program Excel 2007 with calculation of the arithmetic mean (M) and standard error of the mean (m), contingency tables and chi-square test. To assess the significance of differences in average values for characters with a normal distribution, Student t-test was used. The differences were considered statistically significant at $p < 0.05$.

Research results and discussion:

Of the total number of examined (159 patients), signs of atherosclerotic changes in the vessels in the form of an increase in the thickness of the intima-media complex (IMC) over 0.9 mm and detection of intravascular atherosclerotic plaques (AP) (hemodynamically insignificant (h / in- sig) and significant (h / sig)) were observed in 81 people, intravascular AP were detected in 72 people.

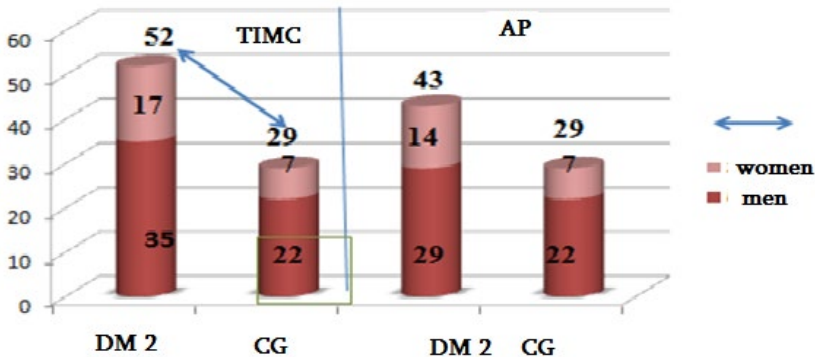


Fig. 2. The number of patients with increased TIMC (>0,9 mm) and AP in patients with and without DM 2

Approximately 14% more often, an increase in TIMC was detected among patients with type 2 diabetes (52 (32.7%) versus 29 (18.24%); $p < 0.01$). Comparatively more frequently, in patients with type 2 diabetes, AP was detected: in 43 patients (27.04%) out of 73 versus 29 cases out of 86 (18.24%) in patients without type 2 diabetes, although the differences were not significant.

Both h/ in-sig and h/sig AP were relatively more common in the subgroup of patients with type 2 diabetes: 34 patients (21.38%) out of 73 versus 23 (14.47%) out of 86 and 9 (5.66 %) of 73 patients versus 6 (3.77%) of 86, although the differences were not significant.

Somewhat more often (unreliably) in the compared subgroups of patients, both an increase in TIMC and AP (in particular, h/sig) were detected in men compared with women.

When analyzing the frequency of detection of AP in different vascular pools in the compared subgroups, certain differences were traced (Fig. 3).

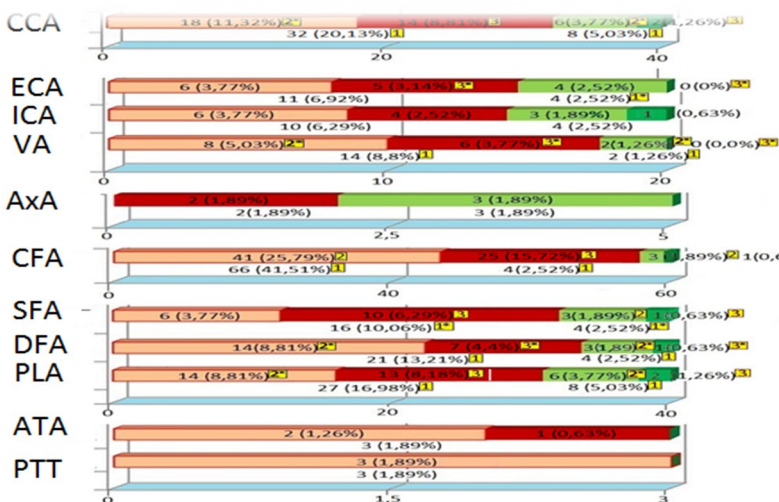


Fig. 3. The frequency of detection of AP in various main arteries in patients with and without type 2 diabetes

The frequency of detection of AP in patients with DM-2 in almost all vascular pools was significantly higher in those with DM-2. Depending on gender, no significant differences were found within the compared subgroups.

In most cases, when examining the vessels of patients, one AP was detected, but some patients formed several (more than 1) AP in one vessel – multiple AP.

Multiple AP was detected only in the subgroup of patients with DM-2, while no cases were registered in the CG.

The frequency of detection of multiple AP in the main arteries on the right and left was as follows (table 1):

Table 1

Frequency of detection of multiple AP in various main arteries in patients with DM-2.

Number of affected vessels	Number of AP	AP h/sig	AP h/in-sig
Common femoral artery (CFA)			
Right	11 (15,07%)	2-5 (34)	4
Left	9 (12,33%)	2-5 (32)	4

Total	20 (27,4%)	66	58	8
Deep femoral artery (DFA)				
Right	3 (4,11%)	2 – 4(10)	9	1
Left	4 (5,48%)	3 – 4 (11)	10	1
Total	7 (9,59%)	21	19	2
Superficial femoral artery (SFA)				
Right	4 (5,48%)	2 – 3 (10)	6	2
Left	2 (2,74%)	2 – 3 (6)	7	1
Total	6 (8,22%)	16	13	3
Popliteal artery (PLA)				
Right	3 (4,11%)	2 – 7 (13)	13	0
Left	4 (5,48%)	2 – 6 (14)	14	0
Total	9 (12,33%)	27	32	0
The posterior tibial artery (PTA)				
Right	1 (0,43%)	2 (2)	2	0
Left	0 (0,0%)	0	0	0
Total	1 (0,43%)	2	2	0
Axillary artery (AxA)				
Right	1 (0,43%)	1(2)	2	0
Left	0 (0,0%)	0	0	0
Total	1 (0,43%)	2	2	0

In 36 (22.64%) patients from the total number of examined patients, multifocal atherosclerosis was observed with simultaneous damage to several vascular pools (table 2)

Table 2.

Frequency of detection of multiple AP in different main arteries in patients with DM-2 with different blood PRESSURE levels

	DM-2 (n = 39)		DM-2 without AH (n = 34)	
NAV	Number of AP		NAV	Number of AB AB
Common femoral artery (CFA)				
Right	9 (12,33%)	30	2 (2,74%)	4
Left	7 (9,59%)	24	2 (2,74%)	7
Total	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
Total	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
Total	5 (6,85%)	12	1(1,37%)	4

Popliteal artery (PLA)				
Right	4 (5,48%)	15	0(0,0%)	0
Left	3 (4,11%)	11	2 (2,74%)	5
Total	7 (9,59%)	26	2 (2,74%)	5
The posterior tibial artery (PTA)				
Right	0 (0,0%)	0	1(1,37%)	2
Left	0 (0,0%)	0	0(0,0%)	0
Total	0 (0,0%)	0	1(1,37%)	2
Axillary artery (AxA)				
Right	1 (1,37%)	2	0(0,0%)	0
Left	0 (0,0%)	0	0(0,0%)	0
Total	1 (1,37%)	2	0 (0,0%)	0

NAV-number of vessels affected by atherosclerotic plaques (AP)

*- reliability of differences between patients with DM-2 and CG (Fisher's exact criterion (two-sided)=0,00783; $p < 0,05$)

Data obtained by us indicates a significant increase in the frequency of combined atherosclerotic changes in several main arteries of various vascular basins in individuals with DM-2 in comparison with patients without DM-2. Thus, in the group of patients with DM-2 out of 73 people, 28 (17.61% of the total number of examined patients) had multifocal atherosclerosis with simultaneous damage to 2 vessels, while in the group without DM-2, combined lesions were observed in only 9 patients (5.66% of the total number of examined patients) ($p < 0.05$) (table 3).

Based on the data obtained, we concluded that the structural and functional features of the walls of large vessels in DM-2 are pathologically changed, which contributes to the emergence and rapid progression of atherosclerotic changes in them with the formation of intravascular AP.

Since vascular remodeling and pathological changes in the inner layers of their walls can significantly affect the nature of intravascular blood flow, we studied the velocity parameters of blood flow: the maximum systolic (MSR) and diastolic rate (DR), as well as the resistance index (RI) (resistance) to blood flow, calculated on the basis of two initial parameters.

There was a clear downward trend in MSR and DR indicators in the CCA system and its branches in patients with. In the vast majority of cases, the differences between subgroups were significant in terms of DR indicators.

Table 3

Frequency of detection of multifocal atherosclerosis in various arteries in subgroups of patients with DM-2 and CG

Indicators	DM-2 (n = 73)		CG (n = 86)	
	MEN(49)	WOMEN(24)	MEN (52)	WOMEN (34)
CL	17(10,69%) ^{2*}	11 (6,92%) ³	7 (4,4%) ^{2*}	(2,52%) ³
TOTAL	28 (17,61%) ¹		9 (5,66%) ¹	
CCA+ECA	4 (2,52%)	3 (1,89%)	1 (0,63%)	0 (0,0%)
Total	7 (4,4%) ^{1*}		1 (0,63%) ^{1*}	
CCA+ICA	4 (2,52%)	3 (1,89%)	2 (1,26%)	1 (0,63%)
Total	7 (4,4%)		3 (1,89%)	
CCA+VA	3 (1,89%)	1 (0,63%)	1 (0,63%)	0 (0,0%)
Total	4 (2,52%)		1 (0,63%)	
CCA+CFA	3 (1,89%)	1 (0,63%)	2 (1,26%)	0 (0,0%)
Total	4 (2,52%)		2 (1,26%)	
CFA+DFA/SFA	2 (1,26%)	2 (1,26%)	1 (0,63%)	0 (0,0%)
Total	4 (2,52%)		1 (0,63%)	
SFA+PLA	2 (1,26%)	1 (0,63%)	0 (0,0%)	1 (0,63%)
Total	3 (1,89%)		1 (0,63%)	

There were no significant differences in blood flow rates in the compared groups of patients, depending on their age.

When selecting a group of patients with elevated IR values, we found that the above indicators were significantly more often increased in patients with DM-2 compared to patients without DM-2, which indirectly indicated the presence of increased vascular stiffness in this category of patients and, accordingly, a greater degree of resistance to intravascular blood flow (table 4).

Table 4

Distribution of patients with and without DM-2 with normal and elevated IR values depending on gender

Indicators	DM-2 (n = 73)		Without DM-2 (n = 86)	
	MEN (n = 49)	WOMEN (n = 24)	MEN (n = 52)	WOMEN (n = 34)
Normal. IR	11 (6,92%) ^{1/3}	7 (4,4%) ^{1/4}	36 (22,64%) ^{1/3*}	32 (20,13%) ^{1/4*}
Total	18 (11,32%) ^{1/2}		68 (42,77%) ^{1/2}	
High IR	38 (23,9%) ^{1/3}	17 (10,69%)	16 (10,06%) ^{1/3}	2 (1,26%)
Total	55 (34,59) ^{1/2}		18 (11,32%) ^{1/2}	

It is known that in vascular (especially internal) remodeling, in addition to TIMC, the intradventitial diameter (IAD) of the arteries also changes, and therefore we also studied this indicator in the examined patient population (table 5).

Table 5

Number of patients with DM-2 and GC (without DM-2) with pathologically altered values of TIMC, IAD and TIMC/IAD.

Indicators	DM-2 (n = 73)		CG (n = 86)	
	MEN(49)	WOMEN(24)	MEN (52)	WOMEN (34)
RIGHT CCA				
TIMC pathology	17 (10,69%) ²	13 (8,18%) ³	3 (1,89%) ²	1 (0,63%) ³
Total	30 (18,87%) ¹		4 (2,52%) ¹	
Left CCA				
TIMC pathology.	10 (6,29%)	8 (5,03%) ^{«3»}	4 (2,52%)	1 (0,63%) ^{«3»}
Total	18 (11,32%) ¹		5 (3,14%) ¹	
Right CCA				
IAD pathology	20 (12,58%) ²	13 (8,18%) ^{«3»}	4 (2,52%) ²	7 (4,4%) ^{«3»}
Total	33 (20,75%) ¹		11 (6,92%) ¹	
Left CCA				
IAD pathology	42(26,42%) ^{2*}	10 (6,29%) ^{«3»*}	4 (2,52%) ²	4 (2,52%) ^{«3»}
Total	52 (32,7%) ¹		8 (5,03%) ¹	
Right CCA				
TIMC/IAD pathology	16 (10,06%) ²	13 (8,18%) ³	3(1,89%) ^{2*}	2 (1,26%) ^{3*}
Total	29 (18,24%) ¹		5 (3,14%) ¹	
Left CCA				
.TIMC/IAD pathology	25 (15,72%) ²	8 (5,03%) ^{«3»}	3(1,89%) ²	1 (0,63%) ^{«3»}
Total	33(20,75%) ¹		4 (2,52%) ¹	

The frequency of detecting an increase in the thickness of the intima-media complex (TIMC) above normal values (more than 0.9 mm) prevailed among patients with DM-2: 30 out of 73 (18.87%)

versus 5 out of 86 (3.14%), respectively. There were no significant differences between the sexes (table).

The average values AND blood PRESSURE in the left and right CCA in patients with the presence and absence of DM-2 were also not significantly different. Pathological values of IAD (below 9.0 mm [Dadova L. V., 2008]) were registered in 52 of 73 patients and in the group with DM-2 and in 11 of 86 patients in the group without DM-2.

Accordingly, a pathological increase in the TIMC/IAD ratio (above 1.20 [Dadova L. V., 2008]) was observed in 33 out of 73 (20.75%) patients with DM-2, while in patients without DM-2 much less frequently - in 5 out of 86 (3.14%) ($p < 0.05$).

The differences revealed by us indicate the earlier formation of disorders of the structure and function of large-caliber arteries in patients with DM-2.

The presence of arterial hypertension (AH) with concomitant DM-2 have led to an increase in the number of patients with atherosclerotic vessels compared to the group of patients with DM-2 without hypertension, and patients without DM-2 with hypertension (table 6).

Table 6

Number of cases of hypertension, CHD, PIX, angina in patients with normal and pathologically altered TIMC/IAD ratio

INDICATORS	Subgroup with DM-2(n = 73)	
	TCIM/IAD norm. (n = 29)	TCIM/IAD pathology. (n = 44)
AH	10 (%)**	29 (%)**
CHD	8 (%)*	30 (%)*
Angina pectoris.	8 (%)	20 (%)
PIX	1 (%)	1 (%)
CHF	2 (%)	1 (%)
Attacks	$1,21 \pm 0,37 (0 - 6)^*$	$2,58 \pm 0,39 (0 - 7)^*$
SToffset	$3,71 \pm 0,7(0 - 13)^*$	$6,13 \pm 0,62(0 - 15)^*$
Homocysteine	$14,79 \pm 1,38(7,2 - 30,8)$	$16,86 \pm 0,95(5,6 - 29,4)$
Endothelin	$8,63 \pm 0,33(6,22 - 12,11)$	$9,46 \pm 0,36(6,22 - 16,32)$

Notes to table 6:

* - *- reliability of differences between patients with DM-2 with normal and pathological TIMC/IAD ratio (student's t-test=2.55; $p = 0.013017$; Chi square test=11.542; $p < 0.001$)

** - ** - reliability of differences between patients with DM-2 with normal and pathological

TIMC/IAD ratio (Fischer's exact criterion (two-way)=0.01581; $p < 0.05$)

The average values of TIMC were significantly higher in comparison with the subgroups with increased blood pressure in both patients with and without DM-2. Indicators and blood pressure were significantly lower, and the TIMC/IAD ratio was significantly higher in the subgroups of patients with hypertension, regardless of the presence of DM-2

The differences we found indicate an additional pathogenic effect of increased blood PRESSURE on the studied parameters, regardless of the presence of DM-2.

In order to assess the impact of previous antihypertensive therapy, we divided each of the groups of examined patients into 2 subgroups, depending on whether antihypertensive therapy was performed on a regular basis (RT) or irregularly (NRT).

In the subgroup of patients with DM-2 and AH ($n = 15$), who did not regularly take antihypertensive drugs, in contrast to patients of the same groups who were constantly treated with antihypertensive drugs, the average values of TIMC CCA were significantly higher.

At the same time, the indicators of IAD and the ratio of TIMC/IAD in patients with DM-2 and AH did not differ significantly, whereas in the group of patients without DM-2, both the indicators of IAD and the ratio of TIMC/IAD was unreliably higher in patients who did not receive regular hypotensive therapy.

When dividing the compared subgroups with DM-2 and CG into internal subgroups with normal and pathologically altered TCIM/IAD ratio, we found a significantly higher number of patients with hypertension, CHD, followed simultaneously with an increase in the number of anginal pain attacks and St segment dislocations of an ischemic nature in the subgroup with a pathologically altered ratio of the studied indicators/

Hence, the indicators of TIMC, IAD and their ratios directly reflect the degree of clinical manifestations of atherosclerosis of

various vascular basins (in particular, coronary), and can serve as a specific marker of possible ischemic cardiovascular complications.

The higher the TIMC/IAD ratio, the greater the likelihood of ischemic episodes and the more severe the clinical course of chronic coronary heart disease in patients with DM-2.

Whereas the arteries are elastic vessels, the decrease in their elastic properties in DM-2 could be due to the rapid development and progression of atherosclerosis and "response" cardiovascular remodeling.

Accordingly, the structural and functional features of the walls of large vessels reflect their subsequent remodeling with the progression of atherosclerotic changes in them and the formation of intravascular atherosclerotic plaques.

In order to assess the vasomotor function of the endothelium, all patients included in the study were subjected to a compression test with reactive hyperemia.

In compliance with the results of the evaluation of the test with reactive hyperemia 15 and 60 seconds after the termination of compression, significantly more frequent pathological variants of the vascular response (considered as endothelial dysfunction (ED) were detected in patients with DM-2/

As far as the presence of AH is a proven factor in the pathogenic development of ED, we divided the groups of patients with DM-2 and CG (without DM-2) depending on the presence of AH, the data obtained are presented in the table. When analyzing data obtained in samples of patients with different blood PRESSURE levels, it was found that the vast majority of cases of DE were observed in the subgroup of patients with DM-2+AH, and in patients without DM-2 – in the sample with increased blood PRESSURE (CG+AH)

Taking into consideration that the paradoxical vascular response was observed only in patients with DM-2 with concomitant hypertension, we reached the conclusion that in this category of patients, the endothelium undergoes significant complex pathogenic

effects, as a result, and a faster development of ED in comparison with patients without DM-2 and AH.

We found no significant differences in the average values of lipid metabolism (LM, GCH, TS, HDL, LDL and VLDL), atherogenicity coefficient (CA), plasma level of homocysteine (HZ) and endothelin-1 (Et-1) in patients with and without DM-2.

However, dividing the total number of examined patients, regardless of the presence of DM-2, into subgroups with variants of normal (positive reaction) and pathological (negative and paradoxical reaction) vascular response during the test with reactive hyperthermia, it turned out that the concentrations of HL, Et-1, as well as GCH, LDL, VLDL, and CA were significantly higher in patients with a pathological endothelial reaction.

Due to the fact that patients with DM-2 often have episodes of "silent" myocardial ischemia (without accompanying pain in the chest), we evaluated cardiac "ischemic" manifestations according to Holter monitoring data. Angina attacks and ST segment displacement episodes of an ischemic nature were significantly more frequent in patients with DM-2: 2.05 ± 0.29 vs. 0.7 ± 0.14 ($p=0.000046$) and 5.21 ± 0.49 vs. 1.13 ± 0.19 ($p=0.00000001$), respectively.

When dividing patients into subgroups with normal and pathological variants of vascular response, it was found that significantly more often hypertension, CHD, and angina were detected in patients with a pathological response (table 7).

Table 7

Average values of plasma concentration of HL, Et-1 and lipid metabolism (M+m) in General and depending on gender in patients with normal and pathological vascular response after a test with reactive hyperemia

Indicators	pathological reaction (n = 74)		normal reaction (n = 85)	
	MALE (n = 48)	FEMALE (n = 26)	MALE (n = 53)	FEMALE (n = 32)
GCh mmol / l	$223,72 \pm 6,16^2$ (152,4 - 333,5)	$234,81 \pm 9,46^3$ (173,45 - 324,6)	$208,37 \pm 3,8^2$ (152,37 - 266,8)	$197,1 \pm 5,46^3$ (130,2 - 252,02)
Totally	$227,62 \pm 5,19$ (152,4 - 333,5) ¹		$204,11 \pm 3,17$ (130,2 - 266,8) ¹	
TF, mmol / l	$8,67 \pm 0,74$ (2,8 - 31,17)	$7,3 \pm 0,51$ (2,54 - 3,88)	$7,72 \pm 0,39$ (3,4 - 16,35)	$7,09 \pm 0,43$ (2,54 - 11,2)
Totally	$8,19 \pm 0,52$ (2,54 - 31,17)		$7,49 \pm 0,29$ (2,54 - 16,35)	

LM, mmol / l	971,19 ± 32,3 (471,7 - 1616,8)	975,84 ± 40,15 (602,6 - 1374,5)	914,04 ± 25,47 (506,4-1336,07)	936,4 ± 39,91 (457,1 - 1374,5)
Totally	972,83 ± 25,38 (471,7-1616,8)		922,46 ± 21,75 (457,1 - 1374,5)	
HDL, mmol / l	42,25± 1,2 (16,88 - 58,6)	45,5 ± 2,75 (34,1 - 8,29)	42,63 ± 1,21 (16,88 - 60,53)	42,29 ± 1,62 (30,21 - 60,91)
Totally	43,39±1,24 (16,88 - 88,29)		42,5±0,96 (16,88 - 60,91)	
LDL, mmol / l	174,45± 5,81 (101,88 - 274,88)	83,64 ± 9,54 ³ (91,73-276,35)	161,77 ± 3,42 (114,93 -227,66)	151,51 ± 5,14 ³ (86,98 - 08,92)
Totally	177,68 ± 5,03 (91,73 - 276,35) ¹		157,9±2,91 (86,98 - 227,66) ¹	
VLDL, mmol / l	15,95± 2,06 ² (1,27 - 70,84)	12,88 ± 1,76 ³ (1,77 - 31,55)	9,02 ± 1,24 ² (1,54 - 37,16)	7,38 ± 1,36 ³ (1,45 - 25,45)
Totally	14,87 ± 1,47 (1,27 - 70,84) ¹		8,41±0,93 (1,45 - 37,16) ¹	
CA	4,49± 0,22 (1,97 - 10,9)	4,44 ± 0,29 (1,04 - 7,87)	4,08 ± 0,17 (2,4 - 10,9)	3,8 ± 0,17 (2,09 - 5,82)
Totally	4,48± 0,17 (1,05 - 10,9) ¹		3,97± 0,13 (2,09 - 10,9) ¹	
HL mmol / l	17,18 ± 1,07 (5,6 - 31,5) ²	18,07 ± 1,46 (5,4 - 29,4)	13,65 ± 1,05 (5,4 - 35,6) ²	15,58 ± 1,75 (5,4 - 36,8)
Totally	17,49 ± 0,86 (5,4 - 31,5) ¹		14,38 ± 0,93 (5,4 - 36,8) ¹	
ET-1, mmol / l	8,83 ± 0,28 ² (6,15-14,24)	9,31 ± 0,5 ³ (6,21-16,32)	7,43 ± 0,15 ² (6,11-11,66)	7,78 ± 0,26 ³ (6,14 - 12,76)
Totally	9,0 ± 0,25 (6,15 - 16,32) ¹		7,56 ± 0,14(6,11 - 12,76) ¹	

In the aspect of searching for optimal means to improve therapy, patients were divided into 3 subgroups depending on the level of blood PRESSURE and the initial functional state of the endothelium.

The first subgroup (subgroup 1) included a part of patients with elevated blood PRESSURE, who registered a pathologically altered vascular response in reactive hyperemia. In this subgroup, only the HGT inhibitor quinapril (accupro) (QP) was added to the traditional hypoglycemic therapy (THT) at a dose of 20 mg 2 times a day with a 12-hour interval, as, firstly, a hypotensive agent, and secondly, a means capable of improving the functional activity of the vascular endothelium [Adasheva T. V. et al., 2013].

In the same subgroup, after a month of QP therapy, verapamil (VRP) with adequate therapeutic effect was added in the next 2 months], in a daily dose of 240 mg.

In the second subgroup (designated as subgroup 2), also composed of patients with diabetes mellitus-2 with elevated blood

pressure, similar to the first in age, gender, and blood pressure levels, fenofibrate was added to the antihypertensive therapy of QP within 1 month, in the next 2 months (Tricor (Tr)), which has a positive complex therapeutic effect, including on the vascular endothelium in a daily dose of 120 mg. Treatment with a combination of QP and Tr lasted up to 6 months.

A re-evaluation of some of the initially studied parameters was carried out after 1 month, 2 months, and 6 months from the date of the initial examination, as various treatment options described above were obtained (table 8)

Table 8

Distribution of patients who received different treatment options

Treatment options	Patients with DM-2 with a pathological reaction		
	Men	Women	Total
1st(TT+QP+VPM)	10	6	16
2nd (TT+QP+Tr)	9	7	16
Total	19	13	32

The dynamics of vascular response and plasma concentration of Et-1 after 1, 3 and 6 months of therapy in these subgroups is shown in table 9

Table 9

Average values of angina attacks per week, St segment dislocations, and the number of abnormal vascular responses detected on the right brachial artery after compression was stopped before and after 3 and 6 months of various therapy options.

Subgroups	Patients with DM-2 with a negative and paradoxical reaction after a compression test with reactive hyperemia (n = 61)		
	1	2	3
Average number (M+m) of angina attacks per week			
Initial	2,63 ± 0,62* (0 - 7) ^{1/3}	3,56 ± 0,63 ^{2/3} (0 - 7)*:**	1,71 ± 0,6* (0 - 7) ^{1/3; 2/3}
In a month	2,44 ± 0,47* (0 - 5)	2,44 ± 0,47*(0 - 5)	1,88 ± 0,6* (0 - 8)

In 2 months.	0,19 ± 0,1* (0 - 1)	0,25 ± 0,11* (0 - 1)	0,18 ± 0,1* (0 - 1)
After 6 months.	0	0,06 ± 0,06** (0 - 1)	0
Average number of St segment offsets (M+m) during ECG monitoring			
Initial	6,13 ± 1,0* (0 - 13)	7,88 ± 1,07* (1 - 15)**	5,53 ± 0,6 (0 - 7)
In a month	4,13 ± 0,67* (0 - 8)	6,06 ± 0,59* (2 - 10)	4,88 ± 0,78 (1 - 9)
In 2 months.	0,75 ± 0,21* (0 - 2)	0,88 ± 0,2* (0 - 2)	0,76 ± 0,18 (0 - 2)
After 6 months.	0,06 ± 0,06 (0 - 1)**	0,25 ± 0,11 (0 - 1)**	0,12 ± 0,08 (0 - 1)**
The number of cases of pathological reaction in the test of reactive hyperemia			
Initial	16 (%)*	16 (%)*:**	17 (%)
In a month	3(%)*	10 (%)*	7 (%)
In 2 months.	0(0,0%)*	0 (0,0%)*	1 (%)
After 6 months.	0(0,0%)**	0 (0,0%)**	1 (%)**

As can be seen from table 14, when both Tr and VPM were added to traditional therapy, the degree of increase in the brachial artery diameter per compression test was almost normalized (a diameter increase of more than 10%), confirming a significant improvement in endothelial function on the example of the brachial artery. In parallel, there was a significant decrease in the number of angina attacks and the number of St segment displacements during ECG monitoring.

CONCLUSIONS

1. In patients with DM- 2, in comparison with persons without DM 2 significantly more often detected both atherosclerotic plaques; in 43 (27,04%) patients with DM 2 vs 29 (18,24%) without diabetes; so are the cases of thickening of the intima-media complex (TIMC) in the main arteries: in 52 (32,7) patients with DM 2 vs 29 (18,24%) without diabetes. Multiple atherosclerotic plaques were detected only in a subgroup of patients with DM2, mainly in the arteries of the lower extremities (in the common femoral artery-21,9% and deep femoral artery-5,5%), they are significantly more often detected in patients with concomitant arterial hypertension (AH). In 37 patients out of the

total number of examined patients, was noted multifocal atherosclerosis with simultaneous damage; in 28 patients with DM 2 (17,6%) and 9 patients without diabetes (5,7%) 2. In patients with DM 2, in comparison with patients without diabetes, in all major vascular pools, there is a decrease in blood flow velocity indicators, combined with an increase in the blood flow resistance index (RI): RI-55 (34,59%) in patients with DM 2 vs 18 (11,32) in patients without diabetes.

3. In patients with DM 2, in comparison with patients without diabetes, there is a violation of the vasomotor function of the endothelium, which is expressed in a decrease in the degree of increase in the diameter of brachial artery after a test of reactive hyperemia: after 15 sec.: $6,45 \pm 0,35$ vs $9,44 \pm 0,25$, after 60 sec.: $7,14 \pm 0,33$ vs $15,2 \pm 0,58$ ($p < 0,0001$). The plasma concentration of endothelin 1 was high in the group of patients with DM 2 in comparison with the comparison group (CG) ($9,1 \pm 0,26$) vs $7,45 \pm 0,11$).

4. In patients with an increased ratio of TIMC/IAD more than 0,120 ($n=44$), the frequency of angina attacks and ST segment displacement of an ischemic nature during Holter ECG monitoring is significantly higher in comparison with patients whose ratio was normal, (39,7% vs 13,7% ($p < 0,05$), which allows using this criterion as a predictive marker of the development of cardiovascular complications.

5. Pathologically altered endothelial response during the test with reactive hyperemia, changed during treatment, with the addition of traditional hypoglycemic and hypotensive therapy with quinapril, tricolor or verapamil, which led to their normalization.

PRACTICAL GUIDELINES

1. Considering the high risk of vascular atherosclerosis in patients with DM-2, it is advisable to use ultrasound Doppler study of the main vascular bed for an adequate non-invasive assessment and appropriate additions to traditional hypoglycemic therapy.

2. Because of the close interrelation of indicators of IMT, IAD and the ratio of IMT/IAD common carotid arteries with cardiac complications in patients with DM-2 appropriate definition of these indicators with the calculation of TIMC/IAD all patients for the purpose of early prediction of cardiovascular complications and their timely targeted pharmacological therapy.

3. In virtue of the significant role of endothelial dysfunction and hyperhomocysteinemia in patients with DM-2, it is advisable to conduct a test with reactive hyperemia and determine the level of homocysteine in the blood with an assessment in dynamics during further therapy.

4. Taking into account the positive therapeutic effectiveness of adding the calcium antagonist verapamil and fenofibrate tricor in the aspect of normalization of endothelial dysfunction, reducing the level of homocysteinemia and endothelin-1, and comparative improvement of coronary blood supply to the myocardium, it is advisable to introduce these drugs into the complex therapy of patients with DM-2 along with hypotensive and hypotensive therapy (in patients with concomitant arterial hypertension).

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LIST OF ABBREVIATIONS

AP - atherosclerotic plaque
AH - arterial hypertension
WHO - World Health Organization
VRP - verapamil
H /sgn - hemodynamically significant
H / in-sign - hemodynamically insignificant
CG - comparison group
HL – homocysteine level
DE - endothelial dysfunction
RI - resistance index
IR - insulin resistance
AC - atherogenic coefficient
QP- Quinapril (Accuid)
MDS - maximum diastolic rate
MSR - maximum systolic rate
MS - metabolic syndrome
DM-2 - type 2 diabetes
TIMC - thickness of Complex of intima-media
Tr - Tricor
XM - Holter monitoring
Et-1 - endothelin-1
HbA1c - glycated hemoglobin
VPM- verapamil

The defense of the dissertation will take place "30 06"
2021 at "14⁰⁰" hours at the meeting ED 2.27 dissertation council,
operating on the basis of the Azerbaijan Medical University

Address: AZ 1022, Baku, st. A. Gasimzade, 14 (administrative
building of AMU, 2nd floor, conference hall.

The dissertation can be found in the library of the Azerbaijan
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on the official website of the Azerbaijan Medical University
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The abstract was sent to the appropriate addresses «27»
05 2021 year

Signed for print: 26.05.2021
Paper format: 60 x 84 ¹/₁₆
Volume: 38 824 characters
Number of hard copies: 20