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Changes in myocardial structure and function in patients with coronary artery disease and type 2 diabetes mellitus

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Abstract

Objective. *Our study aimed to evaluate myocardial structural and functional features in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) compared with patients with CAD without T2DM.*

Methods. *The comparative cohort study included 82 men and 68 women with 2–3 classes of angina. Patients were divided into 4 groups based on the presence of T2DM and their gender. Glycemic status and lipid profile parameters were assessed in all patients. Invasive and non-invasive procedures were performed to assess myocardial and coronary artery structure.*

Results. *Transthoracic echocardiogram (TTE) and electrocardiography (ECG) detected left ventricular hypertrophy (LVH) in 57% of men with CAD and T2DM compared to 35% in those without T2DM. Hypokinetic segments of myocardium were identified on average in 35% of patients (39% men and 34% women) with CAD and T2DM while in patients without T2DM, hypokinesis was detected in 27% of cases (30% men and 23% women). Stenosis of the right coronary artery was detected in 30% of patients with T2DM and in 25% of patients without T2DM. The frequency of coronary artery stenosis in distal segments in patients with T2DM was 3 times higher relative to the non-diabetic group (43% vs 14% in men; 47% vs 16% in women).*

Conclusion. *LV hypertrophy, hypokinetic segments of myocardium and coronary artery stenosis are more predominantly observed in CAD patients with T2DM than in those without T2DM. This should be considered during treatment.*

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Introduction

T2DM is one of the top five diseases with various complications among adults around the world [1]. Experts note its continuous growth in both developed (USA) and developing countries (India, China, Mexico, etc.). According to World Health Organization (WHO), Russia is included in the top ten countries with the highest risk of T2DM. In general, the prevalence of T2DM is from 8 to 10 % [2]. The decrease in average age at the onset of T2DM, potentially associated with lifestyle changes, is of particular concern [3].

Vascular lesions and primarily macrovascular complications predominate among the patients with complications and fatal outcomes of T2DM [4].

It is known that there are 3 types of myocardial damage in patients with T2DM: atherosclerotic coronary lesion, diabetic (metabolic) cardiomyopathy and autonomic neuropathy [2]. Coronary Artery Disease (CAD) is the main cause of death and complications in patients with T2DM [5]. Given these findings, experts tend to consider T2DM as an equivalent to CAD [2]. In addition to the severity of CAD, it is necessary to emphasize the frequency of silent myocardial ischemia in patients with T2DM [6, 7]. Prospective studies have shown that glycemic status is directly associated with macrovascular complications and the prognosis [8, 9].

CAD diagnosis in patients with T2DM, include both invasive and non-invasive methods. This allows to determine further management strategies for patients with CAD and T2DM [10].

Complex assessment of clinical and anatomical myocardial features will allow us to estimate the prognosis and to develop secondary prophylaxis measures in patients with high risk of cardiovascular complications.

Comparative cohort study on myocardial structure and function was performed using invasive and non-invasive procedures to assess the state of myocardium in patients with CAD and T2DM.

Materials and methods

The clinical cross-sectional study after the initial screening (n=180) included 82 men and 68 women with 2–3 classes of angina severity according to the Canadian Cardiovascular Society Angina Grading Scale (1976), who were admitted to the cardiology department of the Domodedovo Central City hospital (Moscow region, Russia). Patients were divided into 4 groups based on the presence of T2DM and gender: group 1 — men with T2DM (n=42), group 2 — women with T2DM (n=38), group 3 — men without T2DM (n=40), group 4 — women without T2DM (n=30). All patients were diagnosed with CAD. The exclusion criteria were: stages 2–4 of chronic heart failure, chronic kidney disease, chronic liver failure, life-threatening heart rhythm disturbances, hypertrophic cardiomyopathy, severe valvular heart disease, type 1 diabetes mellitus, decompensation of T2DM, oncology and blood disorders.

All patients underwent questioning on sociodemographic parameters as well as biological and behavioral risk factors. Patients underwent instrumental and laboratory investigations: blood pressure, resting heart rate, anthropometric parameters (waist circumference, body weight and height with the calculation of body mass index), glycemic status, and lipid profile parameters measurement.

We performed the following invasive and non-invasive studies to determine structural and functional parameters of the myocardium and coronary arteries: standard 12-lead ECG at rest (Schiller AT-10 plus, Switzerland), M- and B-modes TTE (Acuson-128Xp, Siemens, Germany), and invasive coronary angiography (CAG) using GE Innova 4100 apparatus, manufactured in the USA. We also performed polypositional selective CAG of left coronary artery in five standard positions and right coronary artery in three standard positions. We used the Sokolow-Lyon criteria (SV1+ RV5>3.5 mB, RaVL> 1.1 mB) and the Cornell voltage index (>244 mBxmsec) for the diagnosis of LVH using ECG, as well as left ventricular mass index by TTE (>115 g/m² in men, and> 95 g/m² in women).

CAD and the history of myocardial infarction were determined via medical examination, as well as ECG and TTE criteria. The presence of pathological Q or QS wave, ST segment elevation and inverted T wave (along with cardio specific enzymes) were considered as ECG signs of myocardial infarction, inverted T wave with horizontal or oblique ST segment depression —

as CAD. The following parameters were evaluated during CAG: stenosis by segments, by localization, by the degree of narrowing and the frequency of vascular lesions. Informed consent was obtained from all participants prior to the study.

The diagnosis of T2DM was based on patient's historical data, clinical examination, the fasting blood glucose level (over 110 mg/dL for capillary blood, over 126 mg/dL — for venous blood), glycated hemoglobin (≥6,5 %) according to WHO criteria (1999–2013).

Data entry was carried out using ACCESS MS OFFICE system, editing and statistical processing was performed using statistical software SAS version 9.4 (Statistical Analysis System, SAS Institute Inc., USA). Standard criteria were used to determine statistical significance: chi-squared test, Student's t-test for 2 samples and Fisher's exact test for variances. The chosen significance level for all tests was set as $p<0.05$.

Results

Age distribution did not differ significantly among 4 studied groups, and, therefore, could not affect outcomes among groups of patients with and without T2DM. Sociodemographic indicators were also comparable between analyzed groups, with the exception of body mass index, that was significantly higher in patients with T2DM ($p<0.05$), regardless of gender (table 1). Patients with T2DM had hyperglycemia as the level of glycated hemoglobin was by 25 % higher compared with patients without T2DM ($p<0.01$). Smoking rates were lower in men with T2DM compared with non-diabetic group ($p<0.05$).

According to the results of TTE and ECG at rest, LVH was detected in 57 % of men with CAD and T2DM and was 1.5 times lower (35 %, $p<0.05$) in non-diabetic group. We did not reveal statistically significant differences in the frequency of LVH between women with and without T2DM — 40 % and 33 %, respectively (Figure 1).

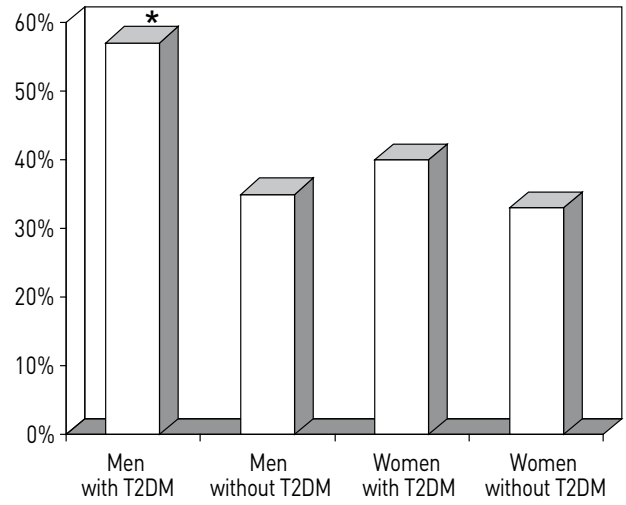

Figure 1. The prevalence of LVH.
LVH — left ventricular hypertrophy, CAD — coronary artery disease, T2DM — type 2 diabetes mellitus, [a]$p< 0.05$ from the result of comparison with other groups.

Hypokinesis of individual myocardial segments according to TTE was detected in 36 % of patients with CAD and T2DM (39 % of men and 34 % of women) and in 26 % of patients without T2DM (30 % of men and 23 % of women). These differences were not statistically significant.

According to TTE data, left ventricular ejection fraction was significantly lower in men and women with T2DM compared with those without T2DM (51.9±1.2 % and 53.4±1.2 %, $p<0.05$).

Table 1. **Clinical characteristics of study patients**

Groups	CAD with T2DM, men (n=42)	CAD with T2DM, women (n= 38)	CAD without T2DM, men (n= 40)	CAD without T2DM, women (n= 30)
Age, years	56.9±0.8	58.4±1.1	57.1±1.1	59.1±1.9
Employment status	Unemployed 15 (36 %)	Unemployed 9 (24 %)	Unemployed 13 (32 %)	Unemployed 8 (27 %)
Smoking	10 (24 %)	4 (10 %)	18 (45 %)*	5 (17 %)
Body mass index, kg/m^2	29.1±0.5*	30.8±0.7*	27.3±0.7	28.4±0.5
HbAc1, %	8.4±0.13**	8.1±0.12*	6.1±0.1	5.9±0.1
Arterial hypertension	31 (74 %)	26 (69 %)	28 (70 %)	19 (67 %)
Average CAD duration, years	6.4±0.5	6.1±0.3	5.9±0.5	5.2±0.4
Average T2DM duration, years	8.2±0.7	7.4±0.4	–	–
Antihypertensive therapy (sartans, ACE inhibitors, beta blockers, calcium antagonists, diuretics)	57.1 %	63.1 %	55 %	63.3 %
Statin therapy (atorvastatin, rosuvastatin)	35.7 %	44.7 %	30 %	40 %
Antiplatelet agents (aspirin, clopidogrel)	80.9 %	81.6 %	80 %	83.3 %
Hypoglycemic agents, including insulin therapy (metformin, sulfonylureas medications)	59.5 %	73.6 %	–	–

ACE inhibitors — angiotensin-converting-enzyme inhibitors, CAD — coronary artery disease, T2DM — type 2 diabetes mellitus, *$p< 0.05$, **$p<0.01$ from the result of comparison between patients with and without T2DM in the same sex group.

Present study included patients who underwent diagnostic CAG with possible further revascularization. The following parameters were assessed: frequency of stenosis by segments, by localization, by the degree of narrowing and the frequency of vascular lesions.

According to CAG, 69 % of men and 50 % of women had stenosis of the anterior interventricular branch of left coronary artery ($p<0.05$ compared with men without T2DM). Stenosis was revealed in 48 % and 32 % of men and women from non-diabetic groups, respectively. Stenosis of the right coronary artery was detected in 30 % of patients with T2DM and in 25 % of patients without T2DM. The stenosis rates of more than 2 coronary arteries were comparable between groups (54 % in patients with T2DM and 45 % in patients without T2DM). The frequency of distal coronary artery segments stenosis in patients with T2DM was 3 times higher compared with patients without T2DM ($p<0.05$) (Figure 2).

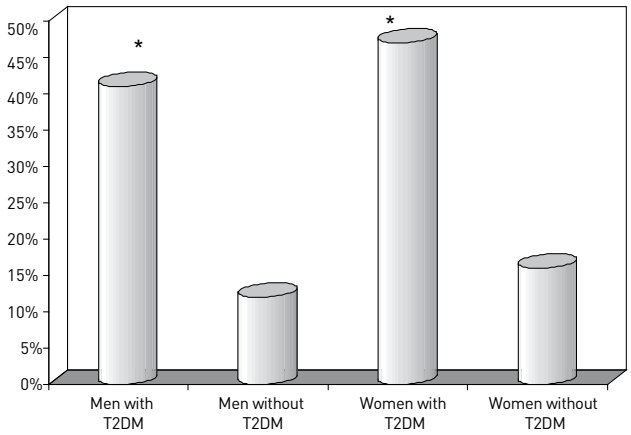

Figure 2. The prevalence of distal segment CAD.
T2DM — type 2 diabetes mellitus, [a] $p<0.05$ from the result of comparison with patients without T2DM in the same sex groups.

Discussion

This study was cross-sectional and aimed to estimate complex clinical and anatomical changes in the myocardium in patients with T2DM. Therefore, we performed comparative analysis of groups of patients with and without T2DM. The groups of patients were comparable by age. In order to assess gender differences, we also compared groups by gender. Thus, the study included 4 groups of patients.

The issue of the study is relevant as the number of patients with acute and chronic CAD among those with T2DM is constantly increasing worldwide [5, 9]. According to the data of multicentral Euroaspire study, the number of new T2DM cases increased when the control of hypercholesterinemia and arterial hypertension significantly decreased compared with previous follow-up studies. In other words, cardiometabolic disturbances and T2DM in particular seem to be the main cardiovascular disease risk factors [2].

Complex assessment of myocardial changes in patients with T2DM is important for the development of complex measures for the prevention of cardiovascular diseases.

The analyzed groups differ by body mass index that indicates the association between overall obesity and T2DM. Lower number of smokers among patients with T2DM can be associated with higher adherence to lifestyle modifications of such patients. People with diabetes are generally more likely to have a chance of education or training for lifestyle changes.

In this study we assessed 2 main aspects that characterize myocardial state: left ventricular hypertrophy and CAG changes. According to experts, only complex diagnostic methods, including imaging methods, can provide additional predictive value when studying the state of myocardium in patients with T2DM [12, 13].

LVH is known to be an independent risk factor for cardiovascular disease that is directly associated with arterial hypertension. Moreover, LVH is one of the main factor that contributes to the development of myocardial dysfunction and heart failure in patients with T2DM [4]. According to the multicenter study, T2DM increases the risk of LVH by approximately 1.5 times which may be associated with abdominal obesity [11]. The frequency of arterial hypertension was comparable between groups. LVH has 1.5 more frequent among men and women with T2DM compared with those without T2DM. Moreover, LVH was associated with the gender and was more pronounced in men with T2DM compared with other groups. This may be associated with 2 main reasons. First, not only arterial hypertension but also neurohumoral components and insulin resistance play a pivotal role in the development of LVH. According to the theory of G Reaven, which describes the association between arterial hypertension and insulin resistance, this state causes a cascade of disturbances including direct effect on target organs [14]. This also highlights the importance of target antihypertensive therapy in patients with LVH and T2DM. In current study most patients received antihypertensive therapy and, obviously, its effect was not so pronounced.

Anatomy of the coronary arteries affect the prognosis of patients with T2DM [15, 16]. Patients with T2DM have several CAD features such as the preva-

lence of painless ischemia that is associated with decreased pain sensitivity in such patients. CAG is still a gold standard diagnostic tool for the diagnosis of CAD including patients with T2DM [17]. Several clinical studies have shown that diffuse coronary artery atherosclerosis, decreased coronary reserve, and multifocal vascular lesions are often observed in such patients [2, 15, 18]. The study showed that the distal coronary arteries lesions predominated in patients with T2DM.

According to the European clinical practice guidelines for acute coronary syndrome, percutaneous coronary intervention is the main revascularization method in patients with T2DM and acute myocardial infarction. It is also recommended to use drug-eluting stents in patients with T2DM. Coronary artery bypass grafting is superior to percutaneous coronary interventions due to common multifocal vascular lesions in patients with T2DM [13, 15]. It should be noted that patients with T2DM often have concomitant diseases (chronic kidney disease and cerebrovascular diseases) that adversely affect coronary revascularization outcomes [2].

Moreover, our study had some limitations. The sample size was relatively small due to inclusion and exclusion criteria. Other limitations included cross-sectional design of the study and the absence of multivariate analysis.

Conclusion

LVH, hypokinetic segments of myocardium and coronary artery stenosis predominated in CAD patients with T2DM than those without T2DM which should be a consideration during treatment. LVH was also associated with gender and predominated in men with T2DM. Multicenter clinical study based on the protocol of our investigation in the future will allow to propose diagnostic algorithms for risk stratification and to develop preventive strategies for the patients with CAD and T2DM.

References

1. Wong N. D., Patao C., Malik S., Iloeje U. Preventable Coronary Aretry Disease events from control of cardiovascular risk factors in US adults with diabetes (projections from utilizing the UKPDS risk engine). Am J Cardiol. 2014; 113:1356–61.doi: 10.1016/j.amjcard.2013.12.042
2. Cosentino F., Grant P. J., Aboyans V., et al. ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020. J; 41:255–323. Doi: 10.1093/eurheartj/ehz486
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014; 37:81–90. Doi: 10.2337/dc14-S081
4. Srinivasan M. P., Kamath P. K., Bhat N. M., et al. Factors associated with no apparent coronary artery disease in patients with type 2 diabetes mellitus for more than 10 years of duration: a case control study. Cardiovasc Diabetol. 2015; 14:146. Doi: 10.1186/s12933–015-0307-z
5. Zafrir B., Jaffe R., Rubinshtein R., Karkabi B., Flugelman M. Y., Halon D. A. Impact of Diabetes Mellitus on Long-Term Mortality in Patients Presenting for Coronary Angiography. Am J Cardiol. 2017; 119(8): 1141–5. Doi: 10.1016/j.amjcard.2017.01.004
6. Tancredi M., Rosengren A., Svensson A. M., et al. Excess Mortality among Persons with Type 2 Diabetes. N Engl J Med. 2015; 373(18): 1720–32. Doi: 10.1056/NEJMoa1504347
7. Valensi P., Lorgis L., Cottin Y. Prevalence, incidence, predictive factors and prognosis of silent myocardial infarction: a review of the literature. Arch Cardiovasc Dis. 2011; 104:178–88. Doi: 10.1016/j.acvd.2010.11.013
8. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352:837–53. https://doi.org/10.1016/S0140–6736(98)07019–6
9. Deedwania P. C. Management of Patients with Stable Angina and Type 2 Diabetes. Rev Cardiovasc Med. 2015; 16:105–13. Doi: 10.3909/ricm0742
10. Eguchi K., Boden-Albala B., Jin Z., et al. Association between diabetes mellitus and left ventricular hypertrophy in a multiethnic population. Am J Cardiol. 2008; 101(12): 1787–91. Doi: 10.1016/j.amjcard.2008.02.082
11. Kowall B., Lehmann N., Mahabadi A. A., et al. Progression of coronary artery calcification is stronger in poorly than in well controlled diabetes: Results from the Heinz Nixdorf Recall Study. J Diabetes Complications. 2017; 31: 234–40. Doi: 10.1016/j.jdiacomp.2016.08.011
12. Price A. H., Weir C. J., Welsh P., et al. Comparison of non-traditional biomarkers, and combinations of biomarkers, for vascular risk prediction in people with type 2 diabetes: The Edinburgh Type 2 Diabetes Study. Atherosclerosis. 2017; 264:67–73. Doi: 10.1016/j.atherosclerosis.2017.07.009
13. Ernande L., Audureau E., Jellis C. L., et al. Clinical Implications of Echocardiographic Phenotypes of Patients with Diabetes Mellitus. J Am Coll Cardiol. 2017; 70:1704–16. Doi: 10.1016/j.jacc.2017.07.792
14. Kowall B., Lehmann N., Mahabadi A. A., et al. Progression of coronary artery calcification is stronger in poorly than in well controlled diabetes: Results from the Heinz Nixdorf Recall

Study. J Diabetes Complications. 2017; 31: 234–40. Doi: 10.1016/j.jdiacomp.2016.08.011

15. Ledru F., Ducimetière P., Battaglia S., et al. New diagnostic criteria for diabetes and coronary artery disease: insights from an angiographic study. J Am Coll Cardiol. 2001; 37:1543–50. Doi: 10.1016/s0735–1097(01)01183–4
16. Scognamiglio R., Negut C., Ramondo A., et al. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. J Am Coll Cardiol. 2006; 47:65–71. Doi: 10.1016/j.jacc.2005.10.008
17. Rivera J.J., Nasir K., Choi E.K., et al. Detection of occult coronary artery disease in asymptomatic individuals with diabetes mellitus using non-invasive cardiac angiography. Atherosclerosis. 2009; 203:442–8. Doi: 10.1016/j.atherosclerosis.2008.07.030
18. Neumann F.J., Sousa-Uva M., Ahlsson A., et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40:87–165. Doi: 10.1093/eurheartj/ehy394