SUMMARY

Diabetes mellitus is a well-known risk factor for myocardial infarction. The purpose of this study was to investigate the prevalence of coronary artery stenosis and collateral blood flow in coronary heart disease (CHD) patients with and without diabetes mellitus. The study included 140 CHD patients, 30 of them with type 2 diabetes mellitus and 110 without diabetes. Coronary arteries were evaluated using selective coronary angiography. Results were compared using Student's paired test and χ²-test where appropriate. Data are presented as mean ± SD. The number of coronary arteries with stenosis was higher in patients with than in those without diabetes (2.7±0.9 vs. 1.9±0.8 per patient, respectively, p<0.005). The mean number of stenoses (in single or multiple coronary arteries) was 3.4±1.5 and 1.9±0.8 in patients with and without diabetes, respectively (p<0.005). Furthermore, diabetic CHD patients showed an increased number of low grade stenosis (less than 50% of vessel diameter) (31.3% vs. 12.8%) and a higher prevalence of total artery occlusion (39.4% vs. 27.3%) (p<0.05 both). Collateral blood flow was found in only 10.3% of diabetic and 41.5% of control subjects (p<0.05), its intensity being 0.14±0.4 and 1.1±1.1 in those with and without DM, respectively (p<0.05). It is concluded that diabetes mellitus is associated with a higher prevalence of coronary artery stenosis, highest prevalence of low grade stenosis and total artery occlusion, and less developed collateral blood flow. These features of coronary artery disease could contribute to the higher incidence and worse outcome of myocardial infarction in patients with diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM) is one of the most important diseases in the modern society and represents not only a medical but also social problem. In industrialized countries, the prevalence of DM is 2%-4% in the general population, and up to 10% in the age group over 65 (1), its incidence showing an increasing tendency. According to estimates of World Health Organization (WHO) experts, a significant increase in DM incidence is expected among persons aged over 25. So, the number of patients of this age group will increase from 135 million to 300 million during the 1995 - 2025 period (2). It has been clearly shown that there are 2 to 2.5 nondiagnosed patients per each registered DM patient, and this takes place at the expense of subjects with type 2 DM. On the other hand, cardiovascular diseases presently are the main cause of death. DM represents an important independent risk factor for the development of and mortality from coronary heart disease (CHD), increasing the risk by 2 to 4 times. According to WHO data, more than 75% of patients with non-insulin dependent DM die due to vascular accidents (3). Taking into account the tendency to population aging observed in the last years in industrialized countries, including Ukraine, the problem of CHD and DM becomes ever more topical.
Naturally, that is why a very great number of investigations have been dealing with elucidation of the reasons of a more frequent development and unfavorable prognosis of CHD in diabetic patients, although much remains unclear till now. Accordingly, the aim of our work was to study the main characteristics in the development and course of CHD in DM patients.

PATIENTS, METHODS AND RESULTS

One hundred and forty patients with clinical signs of CHD, hospitalized at the Department of Endovascular Surgery, Institute of Cardiology, for diagnostic and reconstructive interventions during the 1997 - 2000 period were included in the study. Control group consisted of subjects in whom coronarography showed no atherosclerotic lesions of coronary arteries (n=15). The patients were divided into two groups: CHD patients without DM (n=110) and CHD patients with type 2 DM (n=30). Study groups were matched by age, as mean age was 50.1±4.9 years in the control group, 52.6±8.9 years in the group of non-diabetic CHD patients, and 53.3±6.7 years in the group of diabetic CHD patients (p>0.05). Data are presented as median ± standard deviation (M±SD). A history of myocardial infarction was recorded in 73.3%, and of recurrent infarction in a mean period of 3.0±1.8 years in 54.5% of diabetic patients. In the group of patients without DM, myocardial infarction was recorded in 65.5%, and development of recurrent infarction in 33.3% of patients.

All patients received a generally adopted CHD therapy, taking into consideration the character of the disease course, including aspirin, beta-adrenoblockers, nitrates, inhibitor of angiotensin-converting enzyme, and diuretics.

Selective coronaroven-triculography according to M. Judkins was performed in CHD patients for proper choice of subsequent treatment tactics. On coronarogram analysis, the following parameters were assessed: dominant type of heart blood supply, number of affected arteries, localization of stenoses and their number, degree of stenosis, and presence and characteristics of collateral circulation in the myocardium.

On determination of the dominant type of heart blood supply, based on the estimate of blood supply of the left ventricular posterior wall, we found no significant difference in the prevalence of particular types of blood supply between the two groups of patients. It is known that in case of the right type predominance, blood supply of the left ventricular wall is being realized mainly at the expense of the right coronary artery; in case of the left type prevalence of left type, at the expense of the left coronary artery (its rounding branch); and in case of mixed (balanced) type, at the expense of both arteries. At the same time, the right type of blood supply was dominant in both groups of patients irrespective of the presence of DM, i.e. 42.1% of CHD patients with DM and 55.0% of CHD patients without DM. The left type was less common, i.e. 36.8% and 26.3%, and the balanced type was most infrequent with 21.1% and 18.8%, respectively.

Thus, there is no reason to consider the presence of a certain type of heart blood supply as a determinant in the development of stenosing lesions of great arteries in diabetic patients.

We demonstrated the presence of simultaneous lesions of several coronary arteries in diabetic patients. So, in our study, the mean number of stenosed arteries in the group of diabetic patients was 2.7±0.9 as compared to 1.6±0.6 in the group without DM (p<0.005); lesions to three or more coronary arteries were observed in 66.7% of diabetic patients, which was more than twofold value (30.2%) found in nondiabetic patients. Coronary atherosclerosis in patients with DM was characterized by the presence of multiple lesions located in one artery in both distal and proximal
segments of the vessel. According to our data, coronary vessel narrowings of different degrees were much more often present in the group of diabetic patients, i.e. 3.4±1.5 (from 2 to 7 in one patient) as compared to the same parameter in CHD patients without DM (1.9±0.8; p<0.005). Complete occlusions of two and more coronary arteries were found in 17.3% of diabetic patients (Fig. 1).

We compared and analyzed the prevalence of coronary artery lesions according to the degree of vascular lumen narrowing in patients with and without DM (Fig. 2).

**Figure 2. Degree of stenosis in main coronary arteries**

<table>
<thead>
<tr>
<th>Patients with DM</th>
<th>Patients without DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.1%</td>
<td>18.2%</td>
</tr>
<tr>
<td>39.4%</td>
<td>31.3%</td>
</tr>
<tr>
<td>39.4%</td>
<td>41.7%</td>
</tr>
<tr>
<td>18.2%</td>
<td>12.8%</td>
</tr>
</tbody>
</table>

In the group of diabetic patients, there was a significant increase in the number of hemodynamically insignificant stenoses characterized by <50% arterial lumen narrowing. An increasing tendency was observed in the number of occluded segments in the total number of lesions in diabetic patients as compared with the group of CHD patients without DM (39.4% vs. 27.3%). In CHD patients without DM, narrowing of up to 90% was greatly predominant among the coronary vessel lesions. Such stenoses were 3.8 times more often in the group of patients without DM than in those with DM.

Thus, diabetic patients are characterized by multivascular atherosclerotic lesions with simultaneous stenosing in several coronary arteries, multiple lesions with location of stenoses in proximal and distal parts of the same vessel, predominance of hemodynamically insignificant stenoses, and a tendency to an increasing number of completely occluded segments.

We estimated the prevalence and intensity of coronary collateral circulation in our patients. The study of this characteristic of coronary circulation seemed to be of interest to us, since it is known that collateral circulation as an additional source of blood supply of the myocardium in case of severe coronary bed obstruction, may prove significant and effective in some cases, contributing to the prevention of cardiac ischemia. According to our data, angiographically definable collateral blood flow was noted in 10.3% of diabetic patients and 41.5% of CHD patients without DM (p<0.05) (Fig. 3).

**Figure 3. Collateral blood flow in patients with DM**

<table>
<thead>
<tr>
<th>Patients with DM</th>
<th>Patients without DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.3%</td>
<td>41.5%</td>
</tr>
</tbody>
</table>
At the same time, the intensity of collateral blood flow was much lower in diabetic patients than in CHD patients without DM (0.14±0.4 vs. 1.1±1.1; p<0.05).

There is no doubt that disturbances of the lipid metabolism and coagulation properties of the blood represent the most important links in the development of atherosclerotic vascular lesions in both diabetic and nondiabetic patients (4). Therefore, it seemed to us to be important to study disturbances of the lipid metabolism and homeostasis system in CHD patients with DM as compared to CHD patients without DM, in order to reveal the specific factors contributing to CHD progression in diabetic patients. Thus, blood plasma lipid and lipoprotein fractions: total cholesterol (Ch), triglycerides (TG), low density (LDL) and high density (HDL) lipoproteins, and fibrinogen levels were assessed as parameters reflecting the state of lipid metabolism and rheologic properties of the blood.

Table 1. Blood plasma lipid and lipoprotein fractions and fibrinogen levels in control group and coronary heart disease (CHD) patients with and without diabetes mellitus (DM) (M±SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (n=110)</th>
<th>Patients with CHD (n=62)</th>
<th>Patients with CHD+DM (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.3±0.6</td>
<td>6.0±0.2</td>
<td>6.4±0.2</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.4±0.4</td>
<td>1.8±0.1</td>
<td>2.6±0.1**</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>2.9±0.2</td>
<td>4.1±0.2*</td>
<td>5.0±0.4*</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.3±0.05</td>
<td>1.07±0.03*</td>
<td>0.95±0.03**</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.5±0.22</td>
<td>3.1±0.11*</td>
<td>3.8±0.28*</td>
</tr>
</tbody>
</table>

* p<0.05 as compared with control group;
* p<0.05 data as compared with CHD patients without DM

As shown in Table 1, the mean content of Ch in blood plasma of CHD patients with DM exceeded the range recommended by the European Diabetes Policy Group (5). However, the difference obtained by comparison of this parameter between CHD patients with DM and control group did not reach statistical significance (6.4±0.2 vs. 5.3±0.6 mmol/l; p=0.3). A significant increase in blood plasma triglycerides was recorded in CHD patients with DM as compared to either CHD patients without DM or control subjects (1.4- and 1.9-fold, respectively; p<0.05). Comparison of the quantitative composition of blood plasma lipoprotein fractions revealed that diabetic patients had significantly increased LDL and decreased HDL levels. At the same time, there was no statistically significant difference in LDL level between CHD patients with and without DM. HDL level was lower in CHD patients with DM as compared to CHD patients without DM. The level of fibrinogen was significantly higher in CHD patients with DM than in the control group (by 32.6%; p<0.05). Comparison of blood plasma fibrinogen between CHD patients with and without DM showed an increasing tendency in CHD patients with DM.

DISCUSSION

So, we should first consider the main factors that could, in our opinion, influence the course and type of CHD in diabetic patients. The first and apparently decisive factor would be the considerable number of moderate stenoses found in our study. Their presence is associated with the potential risk of the development of acute coronary syndromes, because ‘recent’ plaques that do not cause lumen stenosis are more susceptible to disruption. Moreover, the probability of instability or disruption of one or more moderate plaques exceeds the risk of instability of several areas with severe stenosis (6). Angiographic investigations indicate that coronary complications take place mostly in the subgroup of plaques rich in lipids, which are mild or moderate in severity, i.e. stenosis does not exceed 50% of the vessel diameter (7). Upon plaque disruption, platelet aggregation increases in this part of the vessel, which leads to further coronary blood flow impairment and may result in thrombotic occlusion of the coronary artery. Moreover, activated platelets at the site of plaque disruption secrete vasoactive substances, which in turn leads to an increase in vasomotor tension and spasms (8). Taking into account the fact that diabetic subjects have endothelial dysfunction and a high probability of secretion of vasoconstrictor substances, the risk of development of coronary spasm and thrombotic occlusion is even more increased. Most diabetic patients show small atherosclerotic lesions along with hemodynamically significant stenosis and occlusions of coronary arteries; therefore, the blood flow slowing down determined by a previous stenosis contributes to platelet adhesion and thrombogenesis. Thus, the characteristics of the atherosclerotic lesions of coronary vessels we found in the presence of endothelial dysfunction in diabetic patients seem to represent one of the possible explanations of a more
common development of coronary hemodynamics in these patients, which clinically manifests itself in unstable angina or myocardial infarction.

On patient coronarogram analysis, we took into account the prevalence and intensity of angiographically determinable collateral blood flow in CHD patients with and without DM. According to our data, angiographically determinable collateral blood flow was noted in a small number of diabetic CHD patients, whereas in the CHD group without DM this parameter was fourfold on an average. On the one hand, the low intensity of collateral blood flow in diabetic patients is probably due to the presence of specific diabetic microangiopathy. Besides this, another important factor of development of collateral circulation in diabetic patients is also the occurrence of myocardial ischemia leading to changes in cell metabolism of the vascular wall in the presence of hypoxia and endothelial secretion of vasodilating substances. This mechanism of collateral formation is likely to be disturbed in diabetic patients because the production of nitric oxide, a potent natural endothelial factor of vascular relaxation, has been proven in diabetic patients (9). On the other hand, it should be stressed once again that in our study a great number of hemodynamically insignificant stenoses were found in the group of diabetic patients, which may also influence the development of collateral blood flow. It is known that the main starting mechanism of collateral circulation development is the perfusion pressure gradient between the areas of the coronary artery up and down the obvious stenosis, i.e. pre- and poststenotic segments, or between the adjacent coronary vessel and distal segment of the stenosed artery. It may be postulated that the predominance of small narrowings of coronary arteries in diabetic patients did not provide a sufficient pressure gradient to increase the inner diameter of collaterals to the size detectable by angiography. Ilia et al. have shown that the intensity of collateral blood flow in persons without DM is generally directly proportional to the number of affected coronary vessels and CHD duration (10). We did not find such a correlation in our diabetic patients, which is in our opinion connected with the low prevalence and intensity of angiographically detectable collateral blood flow in these patients. Therefore, the presence or absence of collateral blood flow in diabetic patients does not reflect the degree of atherosclerotic lesions of coronary arteries, and cannot be considered a marker of coronary atherosclerosis severity in this category of patients. It is known from the literature that the intensity of coronary blood flow, without influencing the prevalence of development of acute CHD complications, is a factor determining the size of the infarction zone. Therefore, the absence of angiographically detectable adequate coronary blood flow reported in our study, along with the progressing development of atherosclerosis of coronary vessels, may be one of the important causes of poor prognosis and worse survival with frequent development of cardiac insufficiency in diabetic patients after myocardial infarction.

At present, the mechanisms of correlation between the dyslipidemia characteristic of diabetic patients and an increase in the risk of development of cardiovascular pathology are being discussed in the literature. In this context, great attention is paid to the study of the causes of a frequently observed combination of the following phenomena known as syndrome X: non-insulin dependent diabetes mellitus, obesity (also observed in our diabetic patients), arterial hypertension, hypertriglyceridemia, hyperinsulinemia, and insulin resistance (11). It is assumed that a decrease in tissue sensitivity to insulin followed by hyperinsulinemia, lipid and lipoprotein metabolism disturbances, and a significant increase in the risk of development of cardiovascular diseases underlie the development of this syndrome. We may suggest the presence of a 'metabolic syndrome' in some of the patients examined, which determined to a considerable extent the character of the changes observed in the coronary vessels.

Today, it is an indisputable fact that the development of acute coronary syndromes such as unstable stenocardia, acute myocardial infarction and sudden coronary death is to a considerable extent prevented by prescribing hypolipidemic therapy to diabetic patients (12,13). As was have already stressed, acute coronary complications occur in the presence of atheromatous plaque instability, which increases the risk of its disruption with efflux of the lipid nucleus content and development - in this context - of parietal thrombosis. At present, there is evidence for an association between lipid content in coronary plaques and their tendency to disruption. It is known that the progressing lipid accumulation worsens coronary atheromatous plaques by fibrous sheath thinning, thus increasing the probability of its disruption. As supposed by a number of investigators, the positive effect of hypolipidemic therapy is just connected with plaque stabilization, which is due to the intranuclear lipid decrease; foam cell count decrease, reduction of the necrotic zone in
the plaque center, and an increase in cell density and collagen content in the fibrous capsule. One of the ways leading to these changes is a long-term (over years) decrease in blood plasma levels of atherogenic lipids and LP, and an increase in HDL content.

The concept according to which the improvement in the clinical course of CHD with hypolipidemic therapy is connected with stabilization of atheromatous plaques that are most susceptible to disruption, has been advanced in FATS study (7). The authors explain CHD aggravations by progressing of hemodynamically insignificant stenoses of coronary arteries. The 'recent' atheromas forming such stenoses contain much lipids, and fibrous capsules are thinned; therefore they are more often the cause of unstable stenocardia and myocardial infarction. Based on the above mentioned, we may assume that the considerable increase in the number of hemodynamically insignificant stenoses (<50% narrowing of the vessel diameter), found in our group of diabetic patients, may explain the high prevalence of acute coronary syndromes in these patients. On the other hand, elimination of cholesterol esters just from these plaques leads to their stabilization and thus to a lesser probability of development of CHD complications. The modern prophylaxis of CHD in diabetic patients is primarily aimed at preventing vascular accidents due to thrombosis and atherosclerosis progression, and is based on the use of preparations whose efficacy has already been demonstrated in many large-scale multicenter studies. Thus, CHD prognosis in diabetic patients depends on many components; the absolute risk of development of acute vascular accidents in diabetic patients is much higher than in patients without DM. Therefore, on trying to influence all the links in the pathogenesis of the disease, we may expect a more significant clinical therapeutic effect in this category of patients.

REFERENCES


