Disturbances of Glucose Metabolism in Men Referred for Coronary Arteriography

Postload glycemia as a predictor for coronary atherosclerosis

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OBJECTIVE — In some studies, fasting and postload glycemia are a strong predictor of coronary events and cardiac death. Therefore, we investigated the relationship between fasting and postload glucose concentrations and coronary status in 363 men referred for coronary arteriography without a previous history of diabetes.

RESEARCH DESIGN AND METHODS — A total of 363 men (mean age 53.0 ± 9.1 years, mean BMI 27.9 ± 3.7 kg/m²) with positive results of exercise testing were included in the study. A standard oral glucose tolerance test (OGTT) with glucose and insulin estimations was performed on all subjects. The concentrations of total cholesterol, HDL cholesterol, triglycerides, and HbA1c were also measured. All patients were divided into four groups, according to coronary status: no changes in coronary arteries (group 0, n = 61), one-vessel disease (group I, n = 113), two-vessel disease (group II, n = 116), and three-vessel disease (group III, n = 73).

RESULTS — The highest postload glucose concentrations were observed in group III. Also, insulin concentrations and HbA1c increased with the progression of atherosclerotic lesions in the coronary arteries. Based on results of the OGTT, 16% of the patients (n = 59) fulfilled the World Health Organization criteria for type 2 diabetes and 36% of the patients (n = 131) met criteria for impaired glucose tolerance. Significant correlations were observed between the number of involved vessels and postload glycemia, HbA1c, fasting insulin, and postload insulin. The multiple stepwise regression analysis showed that age, total cholesterol, and HDL cholesterol independently correlated with the number of involved vessels.

CONCLUSIONS — We conclude that patients with advanced changes in the coronary arteries experience more pronounced metabolic disturbances. Postload glycemia could be an important predictor of nondiagnosed disturbances of glucose metabolism.

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For many years, cardiovascular diseases and especially coronary heart disease (CHD) have been the main cause of premature death in many countries. In addition to the other classic risk factors (smoking, male sex, hypercholesterolemia, and hypertension), diabetes is recognized as an important risk factor for coronary artery disease.

Conversely, the leading cause of mortality in type 2 diabetic patients is cardiovascular disease. Epidemiological data from the Framingham Study demonstrated a two- to fourfold increase in atherosclerotic disease in diabetic patients (1). Also, the risk of death from cardiovascular disease is much higher for patients with diabetes compared with those without diabetes (2). Symptoms of CHD very often precede the symptoms of diabetes. Diabetic patients who have had myocardial infarction have a higher mortality rate in the acute phase of myocardial infarction and in long-term follow-up (3,4). It is believed that type 2 diabetes is very common in patients with CHD, but the true prevalence of disturbed glucose metabolism has not yet been established. Several authors have attempted to evaluate disturbances of glucose metabolism in patients with CHD confirmed by coronary arteriography. In most of these patients, the diagnosis of type 2 diabetes or impaired glucose tolerance (IGT) is based on medical history or a single measurement of fasting glycemia (5,6). The aim of the present study was to estimate the disturbances of glucose metabolism in men with CHD but without a previous history of diabetes who had been referred for coronary arteriography. We also determined whether there is a relationship between the extension of atherosclerosis in coronary angiography and glucose, HbA1c, and insulin concentrations. Additionally, we checked whether the disturbances in glucose metabolism are followed by abnormalities in lipid parameters.

RESEARCH DESIGN AND METHODS — A total of 549 consecutive male patients referred to the Cardiology Department (University Hospital Medical Academy, Białystok, Poland) for coronary angiography between December 1996 and March 1998 were analyzed. The protocol was approved by the Institutional Review Board (Medical Academy, Białystok, Poland), and written informed consent was obtained from all patients. The main aim of this study was to estimate the disturbances of glucose metabolism in men with CHD but without a previous history of diabetes who had been referred for coronary arteriography. We also determined whether there is a relationship between the extension of atherosclerosis in coronary angiography and glucose, HbA1c, and insulin concentrations. Additionally, we checked whether the disturbances in glucose metabolism are followed by abnormalities in lipid parameters.
Assessment of the risk factors of coronary atherosclerosis

Table 1—Clinical characteristics of studied groups

<table>
<thead>
<tr>
<th>Group 0</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>61</td>
<td>113</td>
<td>116</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>48.8 ± 8.8</td>
<td>50.6 ± 8.5</td>
<td>54.0 ± 8.7</td>
</tr>
<tr>
<td>Duration of CHD (years)</td>
<td>3.0 ± 4.6</td>
<td>3.1 ± 4.3</td>
<td>4.1 ± 4.4</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>14 (23.0)</td>
<td>68 (60.2)</td>
<td>83 (71.6)</td>
</tr>
<tr>
<td>Myocardial infarction with Q wave</td>
<td>4 (6.6)</td>
<td>48 (42.5)</td>
<td>71 (61.2)</td>
</tr>
<tr>
<td>Myocardial infarction without Q wave</td>
<td>10 (16.4)</td>
<td>20 (17.7)</td>
<td>12 (10.3)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>24 (39.4)</td>
<td>45 (39.8)</td>
<td>47 (40.5)</td>
</tr>
<tr>
<td>Smoking</td>
<td>24 (39.4)</td>
<td>50 (44.2)</td>
<td>54 (46.6)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>11 (18.3)</td>
<td>20 (17.7)</td>
<td>18 (15.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.9 ± 3.3</td>
<td>27.4 ± 4.2</td>
<td>28.1 ± 3.5</td>
</tr>
</tbody>
</table>

Data are means ± SD or n (%).

Biochemical investigations
In all patients, an oral glucose tolerance test (OGTT; 75-g glucose load) was performed between 8:00 and 10:00 A.M. after an overnight fast, with the patient in a sitting position. The blood samples for glucose and insulin determinations were taken at 0, 60, and 120 min. The diagnosis of diabetes or IGT was made according to the World Health Organization (WHO) criteria. We also used the American Diabetes Association (ADA) criteria to compare the results. Before the test, blood samples were collected for determination of \( \text{HbA}_1c \), total cholesterol (TC), HDL cholesterol (HDL-C), and triglyceride (TG) concentrations. Glucose concentrations were estimated immediately using the oxidase method. Blood serum for insulin determinations was centrifuged and then frozen at a temperature of \(-20^\circ\text{C}\) until assayed. The plasma insulin concentrations were estimated using the immunoradiometric assay method (Polatom, Swierk, Poland). Serum \( \text{HbA}_1c \) levels were determined with high-performance liquid chromatography (HPLC variant; Bio-Rad, Richmond, CA). TC, HDL-C, and TG concentrations were determined with the enzymatic method using commercial kits produced by Analco-GBG (Warsaw, Poland). The concentration of LDL cholesterol (LDL-C) was calculated from Friedewald’s formula: LDL-C = TC – TG/5 (mg/dl).

Coronary angiography
Coronary angiography was performed in patients with symptoms of angina pectoris and positive results of exercise testing. The standard exercise test was performed on a treadmill manufactured by Marquette (Milwaukee, WI). Test results were evaluated in accordance with the typical criteria for positive results of exercise testing. Coronary angiography was performed in the Department of Invasive Cardiology (University Hospital, Medical Academy, Białystok, Poland) using Toshiba *DFP-60A equipment (Shimoishigami, Japan). Patients in whom urgent procedures were required, based on the results of coronary angiography, were not included.

The coronary angiograms were evaluated by experienced cardiologists who were unaware of the glucose tolerance status of the patients. The degree of luminal narrowing was recorded in percentage of prestenotic diameter. Internal luminal narrowing of \(>70\%\) was considered significant, except for the left coronary artery, in which \(50\%\) stenosis was regarded as significant. Based on the results of coronary angiography, patients were divided into four groups according to the number of significant stenoses.

Statistical analysis was performed using Student’s \( t \) test. The comparison of prevalence data among groups was performed by \( \chi^2 \) test. Spearman’s rank correlation analysis and multiple regression stepwise analysis were performed to establish metabolic factors independently related to the number of involved vessels. Data are expressed as means ± SD or \( n \) (%). \( P < 0.05 \) was considered statistically significant.

RESULTS — According to the results of coronary angiography, patients were divided into four groups: no significant stenosis in the coronary arteries (group 0, \( n = 61 \)), one-vessel disease (group I, \( n = 113 \)), two-vessel disease (group II, \( n = 116 \)), and three-vessel disease (group III, \( n = 73 \)) (Table 1).

Based on the results of the OGTT and according to the WHO criteria, 190 patients (52.3%) demonstrated disturbances of glucose metabolism: 131 men (36.1%) had IGT and 59 men (16.2%) had type 2 diabetes. Generally disturbed glucose tolerance was present significantly more often in patients with two- and three-vessel disease (63.9 and 60% of patients, respectively). The statistically significant differences in the prevalence of IGT and type 2 diabetes were observed between the groups (\( 0/II, P < 0.05 \); \( 0/III, P < 0.05 \); \( III, P < 0.05 \); \( III, P < 0.05 \); \( III, P < 0.05 \)) (Table 2). In the patients in group III, type...
2 diabetes was more common, whereas in group II, IGT was more common.

According to the ADA criteria, 37 patients (10.2%) had impaired fasting glucose (IFG), which was defined as FPG between 110 and 125 mg/dl. Only six patients (1.65%) had FPG values between 126 and 140 mg/dl. The remaining cases of diabetes (98.35%) were diagnosed on the basis of postload glycemia. In the group of patients with IGT, 4 patients had no changes in the coronary arteries, 11 patients had one-vessel disease, 12 patients had two-vessel disease, and 10 patients had three-vessel disease; 97.8% of the patients had CHD confirmed by coronary angiography.

Of the six patients with FPG >126 mg/dl, three patients had already been diagnosed with IGT and three patients had been diagnosed with type 2 diabetes according to the WHO criteria. Of the 37 patients with FPG between 110 and 126 mg/dl, 15 patients had been diagnosed previously with IGT and 16 patients had been diagnosed with type 2 diabetes according to the WHO criteria. The six remaining cases had normal glucose tolerance as defined by WHO and IFG as defined by ADA criteria.

The results of fasting glycemia were not statistically different between the study groups (Table 3). None of the 59 diabetic patients had FPG >140 mg/dl. Significantly higher glucose concentrations in 120-min OGGTT were observed in groups II and III compared with groups 0 and I (0/II, P < 0.04; 0/III, P < 0.009; I/II, P < 0.009; I/III, P < 0.01) (Table 3).

The HbA1c concentrations increased progressively with the number of involved coronary arteries and were statistically higher in groups II and III compared with groups 0 and I (0/II, P < 0.05; 0/III, P < 0.02; I/II, P < 0.02) (Table 3).

The atherogenic profile in lipid parameters was observed in patients with two- and three-vessel disease. In these patients, TC, LDL-C, and TG concentrations were statistically significantly higher than in patients without changes in the coronary arteries (Table 3).

Higher insulin concentrations were observed in groups II and III, along with more pronounced disturbances in glucose and lipid metabolism (Table 3). There were significant differences in fasting insulin concentrations between the groups (0/II, P < 0.02; 0/III, P < 0.01) (Table 3).

A statistically significant correlation between the number of involved vessels and HbA1c (r = 0.18, P = 0.0006), post-load glycemia (r = 0.18, P = 0.0004), fasting insulin (r = 0.11, P = 0.039), insulin in 120-min OGGTT (r = 0.15, P = 0.003), and studied parameters of lipid metabolism were observed (TC: r = 0.26, P = 0.0001; LDL-C: r = 0.27, P = 0.0001; HDL-C: r = −0.18, P = 0.0008; TG: r = 0.12, P = 0.018). We also noted marked correlation between fasting insulin and BMI (r = 0.33, P < 0.001) and HDL-C (P < 0.01, r = −0.14). The multiple stepwise regression analysis showed that the factors independently correlating with the number of involved vessels were age, TC, HDL-C; together, these factors explained ~21% of the severity of coronary atherosclerosis. Smoking, hypertension, BMI, glycemia, HbA1c, and insulinemia did not reach statistical significance.

**CONCLUSIONS** — The group of 534 subjects analyzed represents the patients referred for coronary angiography to the Regional Cardiological Center, University Hospital, Białystok, from three districts in northeast Poland during a period of 16 months. The group of 363 patients included in the study was comparable to the average male population with CHD in Poland. The clinical characteristics of patients with CHD in Poland was described in the WHO-MONICA project. The classical risk factors for CHD (age, hypertension, smoking, and obesity) in the Polish MONICA study and in our population were similar (7).

The main findings of our study show that ~50% percent of the studied population, without a previous history of diabetes and with CHD confirmed by coronary angiography, had newly diagnosed disturbances of glucose metabolism (IGT or type 2 diabetes). The prevalence of diabetes was 16% and was much higher than the prevalence of diabetes in the general population in Poland, which is ~2–4% (8). Similar results were obtained by Farrer et al. (9), who estimated the disturbances of glucose metabolism in male patients undergoing elective coronary artery bypass grafting. In this study, ~30% of the patients had

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**Table 2** — The prevalence of disturbances of glucose metabolism in the studied groups

<table>
<thead>
<tr>
<th></th>
<th>Group 0</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>61</td>
<td>113</td>
<td>116</td>
<td>73</td>
</tr>
<tr>
<td>Normal</td>
<td>36 (59)</td>
<td>65 (57.9)</td>
<td>43 (37.1)</td>
<td>29 (39.7)</td>
</tr>
<tr>
<td>IGT</td>
<td>22 (36)</td>
<td>35 (30.9)</td>
<td>55 (47.1)*</td>
<td>19 (26.0)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (4.9)</td>
<td>13 (11.5)</td>
<td>18 (15.5)</td>
<td>25 (34)**</td>
</tr>
</tbody>
</table>

Data are n (%). *P < 0.05 group 0 versus respective value in groups I, II, and III; †P < 0.05 group I versus respective value in groups II and III.

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**Table 3** — Lipid, glucose, insulin, and HbA1c concentrations in the studied groups

<table>
<thead>
<tr>
<th></th>
<th>Group 0</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>204.4 ± 29.5</td>
<td>220.7 ± 38.0</td>
<td>225.9 ± 36*</td>
<td>231.8 ± 30.1†</td>
</tr>
<tr>
<td>LDL-C</td>
<td>129.4 ± 29.8</td>
<td>145.5 ± 34.4*</td>
<td>149.8 ± 32.6*</td>
<td>157.3 ± 26.5**</td>
</tr>
<tr>
<td>HDL-C</td>
<td>43.2 ± 10.2</td>
<td>40.0 ± 10.8</td>
<td>38.1 ± 11.0</td>
<td>37.3 ± 10.3*</td>
</tr>
<tr>
<td>TG</td>
<td>158.3 ± 49.2</td>
<td>170.9 ± 77.5</td>
<td>193.5 ± 88.0**</td>
<td>191.5 ± 91.6*</td>
</tr>
<tr>
<td>Glucose 0min</td>
<td>91.2 ± 10.7</td>
<td>93.6 ± 15.8</td>
<td>93.4 ± 12.6</td>
<td>93.4 ± 12.9</td>
</tr>
<tr>
<td>Glucose 60min</td>
<td>171.2 ± 37.1</td>
<td>167.6 ± 42.3</td>
<td>172.6 ± 35.0</td>
<td>179.1 ± 40.9</td>
</tr>
<tr>
<td>Glucose 120min</td>
<td>141.2 ± 36.8</td>
<td>139.3 ± 46.4</td>
<td>154.5 ± 40.1**</td>
<td>163.1 ± 54.9**†</td>
</tr>
<tr>
<td>Insulin 0min</td>
<td>7.3 ± 4.3</td>
<td>9.8 ± 4.7</td>
<td>10.0 ± 10.6</td>
<td>10.5 ± 7.6*</td>
</tr>
<tr>
<td>Insulin 60min</td>
<td>93.3 ± 61.6</td>
<td>108.5 ± 77.0</td>
<td>103.7 ± 70.8</td>
<td>111.8 ± 81.0</td>
</tr>
<tr>
<td>Insulin 120min</td>
<td>70.3 ± 60.3</td>
<td>70.9 ± 64.9</td>
<td>84.8 ± 59.7</td>
<td>91.0 ± 66.3†</td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.7 ± 0.5</td>
<td>5.9 ± 0.58</td>
<td>5.9 ± 0.47*</td>
<td>6.1 ± 0.53**†</td>
</tr>
</tbody>
</table>

Data are means ± SD. *P < 0.05 group 0 versus respective value in groups I, II, and III; †P < 0.05 group I versus respective value in groups II and III.
disturbances of glucose metabolism: 6% previously diagnosed diabetes, 4% newly diagnosed diabetes, and 20% IGT. The diagnosis of diabetes and IGT was made after OGTT according to the WHO criteria. The prevalence of diabetes was 10%, which is also much higher than in the respective general population. Also, in other studies in which OGTT was performed, the prevalence of IGT and diabetes was much higher. In a study of a Japanese population with CHD confirmed by coronary angiography, the prevalence of disturbances of glucose metabolism was very high (67.7%): IGT was noted in 32.3% of the patients and type 2 diabetes was diagnosed in 35.4% (10). The prevalence of IGT was similar in our study (36%). The higher prevalence of diabetes in a study by Fujisawa et al. (10) can be explained by the fact that patients with diagnosed diabetes controlled by diet were included in the analysis. Also, Seibaek et al. (11) reported the high frequency of disturbances of glucose metabolism in men referred for coronary angiography. In these patients, the abnormal glucose tolerance was present in 37.4% of patients and was statistically higher than in the general population (11).

The prevalence of abnormal glucose tolerance was markedly lower in the studies in which the diagnosis was based on the medical history or FPG measurement. In the multicenter Coronary Artery Surgery Study, the prevalence of diabetes was 12.9% in patients older than 50 years of age (diagnosis based on clinical history) (12). In the study by Freedman et al. (6), 8% of patients with CHD confirmed by coronary angiography had diabetes (diagnosis of diabetes based on fasting glyce mia). In a recently published analysis of 2,253 subjects who underwent coronary angiography from 1982 to 1992, 269 patients (12%) had diabetes; most cases (86%) had been diagnosed previously. In the remaining 14% of patients, diabetes had been newly diagnosed on the basis of FPG >126 mg/dl on two separate occasions (5).

In our study, we observed that the prevalence of IGT or type 2 diabetes increases with the progression of atherosclerotic lesions in the coronary arteries. Also, Ferrannini et al. (5) reported a higher prevalence of coronary stenosis in diabetic patients, especially in those with three-vessel disease (13).

In our study, fasting glucose concentrations did not differ between the study groups. However, there was a significant difference in glucose concentrations in 120-min OGTT, with the highest value demonstrated in patients with three-vessel disease. Postload glycemia correlated significantly with the extension of atherosclerosis observed in the coronary angiograms.

Several studies have attempted to find the link between hyperglycemia and the development of coronary atherosclerosis. The first prospective observation that pointed out the role of hyperglycemia in CHD was the Framingham Study, which showed that the incidence of cardiovascular disease is two- to threefold higher in diabetic patients (1). However, this study compared patients with diabetes and nondiabetic subjects. A Paris Prospective Study was conducted in healthy men aged 44–55 years with no prior history of diabetes. They underwent a standard OGTT and were then followed for a mean period of 23 years from enrollment. In this study, the authors showed that an increase in either fasting or 2-h glucose levels predicted significant increases in the mortality rate from CHD as well as total mortality (14,15).

Another parameter that reflects glucose concentrations widely accepted in clinical practice is HbA1c. It was observed that HbA1c, even in the upper limits of normal range, could be a predictor of coronary events (16,17), independent of other known risk factors. The prognostic value of HbA1c was observed also in the Rancho Bernardo Study (18). Another study (16) showed that there is a significant increase in the risk of death and all coronary events in patients with HbA1c >7%, compared with diabetic subjects with lower value of glycated hemoglobin. In our study the highest mean value of HbA1c was observed in men with more pronounced changes in the coronary arteries. We also noted a significant correlation between glycated hemoglobin and the number of involved vessels, which supports the hypothesis that HbA1c is one of the more important prognostic factors in coronary artery disease (16,17).

Data from a number of studies suggest that hyperinsulinemia may be an independent risk factor for cardiovascular and CHD mortality (19,20). For instance, a 22-year follow-up in the Helsinki Policeman Study (21) showed that hyperinsulinemia predicted CHD in healthy middle-aged men (34–64 years of age) who did not have a history of diabetes. The impact of hyperinsulinemia on the development of CHD was independent of other known risk factors: obesity, glyce mia, smoking, hypertension, or hypercholesterolemia.

In our study, patients with more pronounced atherosclerotic lesions in the coronary arteries (two- and three-vessel disease) without a previous history of diabetes had significantly higher fasting and postload insulin concentrations. We also showed a significant positive correlation between fasting and postload insulin concentrations and the number of involved vessels in coronary angiography. Contrary to these results, Seibaek et al. (11) did not show any correlation between insulin and the number of involved vessels in coronary angiograms. However, they observed significantly higher insulin concentrations in patients with CHD and type 2 diabetes or IGT compared with the control group (11).

Another potential factor by which hyperinsulinemia/insulin resistance could influence the development of CHD is dyslipidemia, which consists of increased TG, decreased HDL-C, increased small LDLs, and apolipoprotein abnormalities (22). Some authors suggest that insulin resistance/hyperinsulinemia could be considered as a risk factor for coronary artery disease, but only if they are accompanied by increased TG concentrations and diminished HDL-C concentrations (20,23). In the present study, men with significant changes in the coronary arteries had significantly higher TG, LDL-C, and TG concentrations and lower concentrations of HDL-C compared with the group without changes in the coronary angiograms. Moreover, both Spearman’s rank correlation and multiple stepwise regression analysis showed a significant correlation between the number of involved vessels and the studied parameters of lipid metabolism.

In view of the discussed articles and our results, disturbances in glucose metabolism play an important role in the pathogenesis of CHD. They are recognized too late when diabetic vascular complications are present. We believe that most unrecognized disturbances of glucose metabolism could be explained by the use of single measurements of FPG in the diagnosis of diabetes. Therefore, we conclude that the measurement of post-
prandial rather than fasting glycemia should be recommended for an early identification of patients who are at higher risk of coronary events.

References