Coronary Artery Disease, Microalbuminuria and Lipid Profile in Patients with Non-Insulin Dependent Diabetes Mellitus

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Purpose – To determine the frequency of coronary artery disease, microalbuminuria and the relation to lipid profile disorders, blood pressure and clinical and metabolic features.

Methods – Fifty-five type 2 diabetic patients (32 females, 23 males), aged 59.9±9 years and with known diabetes duration of 11±7.3 years were studied. Coronary artery disease (CAD) was defined as a positive history of myocardial infarction, typical angina, myocardial revascularization or a positive stress testing. Microalbuminuria was defined when two out of three overnight urine samples had a urinary albumin excretion ranging 20-200µg/min.

Results – CAD was present in 24 patients (43.6%). High blood pressure (HBP) present in 32 patients (58.2%) and was more frequent in CAD group (p=0.05) HBP. Increased the risk of CAD 3.7 times (CI[1.14-12]). Microalbuminuria was present in 25 patients (45.5%) and tended to associate with higher systolic blood pressure (SBP) (p = 0.06), presence of hypertension (p = 0.06) and know diabetes duration (p = 0.08). In the stepwise multiple logistic regression on the systolic blood pressure was the only variable that influenced UAE (r = 0.39, r² = 0.14, p = 0.01). The hypertensive patients had higher cholesterol levels (p = 0.04).

Conclusion – In our sample the frequency of microalbuminuria, hypertension, hypercholesterolemia and CHD was high. Since diabetes is an independent risk factor for cardiovascular disease, the association of other risk factors suggests the need for an intensive therapeutic intervention in primary and in secondary prevention.

Keywords: coronary artery disease, microalbuminuria, lipid disorders, diabetes mellitus
disease and lipid and blood pressure parameters in a
group of patients with NIDDM regularly treated at the
diabetes outpatient facility of the Hospital Universitário
Pedro Ernesto.

Methods

Fifty-five patients with NIDDM were studied (32
women and 23 men, mean age 59.9±9 years). Their mean
known duration of the disease was 11.47±3 years; 7
were smokers and 48 were nonsmokers. They were regularly
seen at the diabetes outpatient center. Patients with sys-
temic infections, heart failure and renal failure were exclu-
ded (by the presence of hematuria, abnormal sediment or
plasma creatinine >1.5mg/dL, without proteinuria).

Forty patients used insulin in alone or in combination
with oral hypoglycemic agents and 15 used only oral
antidiabetic drugs. Patients received written instructions to
collect three nocturnal urine samples in a maximum six
month interval, maintaining the same diet prescribed (55/
60% carbohydrates, 25/30% lipids and 15/20% proteins)
and activity level in the period. After a 12-hour fast, two
venous blood samples were collected, on different days, for
the analysis of the following variables: total cholesterol
(reference value RV) <220mg/dL; triglycerides (RV: 40/
160mg/dL) and HDL-cholesterol (RV: 35/55mg/dL), glucose
(RV: 70/110mg/dL) and glycated hemoglobin (HbA1c) (RV:
4.5/6.2%). Thrombosis, cholesterol/HDL and LDL/HDL were
considered good glycemic control; values 1.33 to 1.5, average
values were 1.67. Microalbuminuria had a trend toward higher SBP (152±18.7 vs 142.7±16.9mmHg, p=0.06), for a greater prevalence of hyper-
tension when in the use of antihypertensive medications.
The anti-hypertensive medication was not modified in any
patient during urine sample collection.

Forty-three patients underwent a treadmill stress test,
using the Bruce protocol, the Quinton treadmill (model Q55)
and a computerized real time stress ECG analysis system
(Micromed v.2.1). Medications that could interfere with test
results were withdrawn 48hs prior to the test. Clinical
hemodynamic and electocardiographic criteria for effort-
induced ischemia were those of the Brazilian Consensus on
Ergometry and Rehabilitation.

Statistical analyses were performed using the Mann-
Whitney test for two independent samples with abnormal
distribution and Student’s t test for the comparison of two
independent samples with normal distribution. Chi-square
test with the Yates correction was used for categorical varia-
tables. For the stepwise logistic regression the abnormally
distributed variable underwent a logarithmic transformation.
Data were presented as mean ± standard deviation or median
(minimum-maximum) and p<0.05 was considered significant.
SPSS (version 6.0) and Epi Info (version 6.0) programs were
used. Frequencies are presented along with confidence in-
tervals (CI).

Results

Patients’ clinical characteristics are shown in table 1.
Of 55 studied patients, 25 (45.5%, CI [32.9-59.5]) had
microalbuminuria and 30 (54.5%, CI [40.6-67.8]) hadnormal
albuminuria. UAE values were, respectively, 32.2 (17.5-
108.7) vs 9.6 (1.6-20.6) µg/min. Patients with microal-
buminuria had a trend toward higher SBP (152±18.7 vs
142.7±16.9mmHg, p=0.06), for a greater prevalence of hyper-
tension (72% vs 46.7%, p=0.06) and for a great known dura-
tion of the disease (12.4±7 vs 9.7±7.7 years, p=0.08) than
patients with normal albumin excretion. Other studied varia-
tables were not statistically different (tab. I). Stepwise regres-
sion analysis indicated that the only variable associated with
UAE was systolic blood pressure (r=0.39, r²=0.14, p=0.01).

Hypertension was present in 32 patients (58.2%, CI
[41.4-71]), and 30 patients were on medication (93.7%).
The most used drugs were: angiotensin-converting enzyme
inhibitors (14 patients), alone or in association, and calcium
channel blockers, isolated or in association (16). Average
systolic blood pressure was 146.9±18.2mmHg and diastolic
blood pressure was 85.1±9.4mmHg. Despite treatment, 19
(59.4%) patients had systolic ≥140mmHg and diastolic
Coronary heart disease, microalbuminuria in type 2 diabetic patients

Mean lipid levels in the total diabetic group were: cholesterol 230.4±82.2 mg/dL, triglycerides 152.5±86.2 mg/dL, HDL-cholesterol 53.2±19.1 mg/dL, LDL 146.7±46 mg/dL, cholesterol/HDL 4.9±2 (females 4.6±1.9; males 5.2±2) and LDL/HDL 3.2±1.6 (women 2.9±1.5; men 3.5±1.7) (tab. II). 38 patients (69.1%, CI [55-80.5]) had cholesterol >200 mg/dL; 11 (20%, CI [10.8-33.4]) had triglycerides >200 mg/dL; 9 (16.4%, CI [8.2-29.3]) had HDL <35 mg/dL and 35 (63.6%, CI [50.3-75.5]) LDL >30 mg/dL. Hypertensive patients had higher cholesterol levels compared with normotensive patients (240.8±51.6 vs 215.9±36.7 mg/dL, p=0.04). Women had higher HDL-cholesterol levels than men did (56.4±17.4 mg/dL vs 48.7±20.9 mg/dL, p=0.02).

With regards to glycemic control, 21 (38.2%) patients had good control, 11 (20%) had average control and 23 (41.8%) had poor control. Patients with cholesterol >200 mg/dL had a tendency toward worse metabolic control (p=0.05). Differences in other parameters were not observed.

Obesity was observed in 29% of the patients (n=16) and overweight in 52.7% (n=19), a total of 81.8% of the sample above ideal weight. These patients had higher cholesterol (236.7±49.3 vs 202.1±30.5, p=0.02), triglycerides (163.2±91 vs 104.2±30.7, p=0.01), LDL (153.8±45.7 vs 114.6±32.4, p=0.008), diastolic blood pressure (86.3±9.2 vs 79.8±9, p=0.05) and lower HDL levels (50.2±16.1 vs 66.6±26, p=0.05). We observed a greater prevalence of hypertension in overweight patients (64.4% vs 30%, p=0.04). The presence of CAD was similar in obese and nonobese patients.

Discussion

The present study is a transverse cohort study of a...
population with NIDDM treated at a University Hospital, a reference center for the State of Rio de Janeiro.

Transverse cohort and longitudinal studies have demonstrated that microalbuminuria is a predictor of large vessel disease. Many factors contribute to this: race, diabetes duration, microalbuminuria criteria and size and design of the studies. Similar to the present study, several other reports in the literature associate microalbuminuria with systolic blood pressure. The association with diastolic blood pressure is less evident. It is important to emphasize that the association is also described in nondiabetic populations, suggesting the presence of a relation with the high insulin resistance syndrome. The association with the duration of diabetes is also controversial, with studies showing microalbuminuria in recently diagnosed patients. This could be explained by the fact that in most patients with NIDDM the duration of the diabetes is unclear. The frequency of microalbuminuria in our group was 45.5%, with a tendency for increased systolic blood pressure, duration of the diabetes and hypertension in type 1 stepwise multiple regression analysis. Systolic blood pressure was the only variable that significantly influenced the rate of UAE. We did not observe a relation between HbA1c and microalbuminuria, sometimes reported or not in the literature. Possibly, transverse cohort studies, such as ours, are less likely to reveal the influence of glycemic control on the development of microalbuminuria.

Confirming other reports in the literature, the frequency of hypertension in our sample was 58.2%, being more common in patients with microalbuminuria and overweight. We observed that 19 (59.4%) treated patients still had blood pressure levels over 140/90 mmHg, in spite of the fact that 43% of them had already been using two or more antihypertensive drugs, demonstrating inadequate pressor control, according to the levels suggested by the American Diabetes Association and the Joint National Committee. This information is relevant because, in a recent multi-center study, diabetic patients who maintained diastolic blood pressure <80 mmHg had lower mortality and cardiovascular events. The high prevalence of hypertension among patients with normal UAE suggests, possibly, the presence of essential hypertension not related to incipient diabetic or clinical renal disease. This is not observed in type 1 diabetic patients who present hypertension in advanced phases or clinical renal disease.

The presence of diabetes increases the risk of CAD two-to-four fold in comparison with the risk in the general population. There are, however, large differences in the prevalence of risk for CAD among different countries. This was evaluated in a multi-center study on vascular disease in diabetic patients sponsored by the World Health Organization, which followed 4,714 patients for 10 years studying causes of death and risk factors. There was a large variation in the prevalence of CAD and, despite that these patients had a greater frequency of hypertension and lipid disorders, the main independent risk factor for coronary disease was the presence of proteinuria. Other transverse population studies in diabetic patients demonstrated that cardiovascular risk depends on race. Thus, American Pima Indians and Japanese have a lower risk than the American white population, suggesting genetic and environmental differences in the prevalence of CAD. The classical results reported in the Framingham study suggest that the presence of risk factors adversely affects the development of macrovascular disease both in nondiabetic and NIDDM patients. In our group, CAD frequency was 43.6%, similar to the 40 to 50% reported in the literature. We observed that there was a greater prevalence of hypertension in these patients, with a risk ratio of 3.7 for coronary disease, confirming prior reports in the literature. This is important because cardiac mortality among diabetic patients increases three-fold when there is associated hypertension. Several studies demonstrated the association of CAD with microalbuminuria, which was not observed in our sample.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Positive coronary artery disease</th>
<th>Negative coronary artery disease</th>
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<tbody>
<tr>
<td>Number</td>
<td>24</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>11/13</td>
<td>20/11</td>
<td>0.16</td>
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<tr>
<td>Age (years)</td>
<td>61.2±10.2</td>
<td>58.7±7.8</td>
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<tr>
<td>Diabetes duration (years)</td>
<td>12.5±3.3</td>
<td>9.72±7.2</td>
<td>0.16</td>
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<tr>
<td>Glycated hemoglobin (%)</td>
<td>8.6±3.6</td>
<td>8.7±2.4</td>
<td>0.93</td>
</tr>
<tr>
<td>Metabolic control index</td>
<td>1.4±0.25</td>
<td>1.4±0.4</td>
<td>0.93</td>
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<tr>
<td>Cholesterol</td>
<td>230±64</td>
<td>230.7±51.8</td>
<td>0.98</td>
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<tr>
<td>Triglycerides</td>
<td>163.4±103.2</td>
<td>144.7±70.9</td>
<td>0.52</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>50±17.8</td>
<td>55.6±20</td>
<td>0.18</td>
</tr>
<tr>
<td>LDLc (mg/dL)</td>
<td>147.3±40.2</td>
<td>146.3±50.6</td>
<td>0.62</td>
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<tr>
<td>UAE (µg/min)</td>
<td>18.6 (3.7-108.7)</td>
<td>14.1 (1.6-85)</td>
<td>0.12</td>
</tr>
<tr>
<td>SBP</td>
<td>152.6±17.6</td>
<td>142.6±17.7</td>
<td>0.03</td>
</tr>
<tr>
<td>DBP</td>
<td>86.7±9.7</td>
<td>83.9±9.2</td>
<td>0.26</td>
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<tr>
<td>HBP - n (%)</td>
<td>18 (75)</td>
<td>14 (45.2)</td>
<td>0.05</td>
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<tr>
<td>Obesity - n (%)</td>
<td>20 (83.3)</td>
<td>25 (80.6%)</td>
<td>0.90</td>
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</tbody>
</table>

Data are presented in mean ±SD or average (minimum-maximum). UAE - urinary albumin excretion; BMI - body mass index; CAD - coronary artery disease; SBP - systolic blood pressure; DBP - diastolic blood pressure.
Although we cannot exclude a type 2 error, due to the size of the sample, other reports in the literature stress that CAD is associated mainly with macroalbuminuria and not microalbuminuria\(^4\)-\(^8\),\(^14\)-\(^30\),\(^32\). Possibly, this divergence with the literature, excluding data inherent to the studied population, is due to different methods and criteria for coronary disease and microalbuminuria diagnoses.

In the lipid analysis we did not use the criteria recommended by the Brazilian Consensus on Lipid Disorders\(^36\), since those criteria were not based on the Brazilian diabetic population. In our group, the prevalence of hypertriglyceridemia and low HDL levels was similar to that reported in the literature\(^37\),\(^38\). Frequency of hypertriglyceridemia seems larger in recently diagnosed patients and during phases of acute decompensation. We observed a high prevalence of hypercholesterolemia and increased LDL levels. Some factors can explain this finding, such as increased age of the study population (some studies demonstrated that LDL levels increase with age after 50-55 years in men and 60-65 in women\(^14\),\(^39\)) increased consumption of saturated fat and cholesterol in the diet, which was not assessed in our study, and the presence of genetic lipid disorders. If we adopt the recommendation of LDL <100 mg/dl, as proposed for patients with macrovascular disease, 90.9% of our sample would be characterized as having dyslipidemia (n=50), which would call for an intense secondary prevention effort. Patients with hypercholesterolemia had a tendency for worse glycemic control. A similar finding was not observed in patients with hypertriglyceridemia (possibly because only 11 (20%) patients had this lipid disorder. We believe that the influence of glycemic control on lipids should be analyzed in large prospective studies, especially with the allocation of patients to intensive and conventional treatment groups. A study observing this design did not demonstrate influence of the glycemic control on different lipid parameters after a 30-month follow-up of patients with NIDDM\(^40\). Data from a longitudinal study in the United Kingdom (UKPDS) have provided information with respect to the relation between these events. However, it is important to emphasize that glycemic control can influence specific phases of the metabolism of lipids, such as the reverse transport of cholesterol. Recently, it was demonstrated that the glycation of HDL, especially the subfraction HDL\(_2\), favors a faster and more efficient transfer of cholesterol from this fraction to apoprotein B-containing lipoproteins\(^41\). We did not observe an association between lipid disorders and CAD, as described in studies with diabetic and nondiabetic patients\(^39,42,43\). Possibly isolated lipid determinations are not enough to detect the association of these events. This finding was observed in studies in populations from Europe and Brazilian private practices\(^39\), which included diabetic patients and used diagnostic criteria for CAD and lipid disorders similar to those of our study. We know, today, that there are several other factors, genetic and nongenetic, that can influence the basic process of the disease, i.e. atherosclerosis, such as the apolipoprotein B and paraoxonase genetic polymorphism\(^44\), the presence of lipoprotein (a)\(^37\), increased oxidized LDL and its affinity to proteoglycans of the intimal layer of the vessel wall\(^45\). These factors could trigger different responses in the endothelium that would favor the development of atherosclerotic plaques.

We conclude that patients with NIDDM, treated in a tertiary care center, had a high prevalence of incipient renal disease, hypertension, hypercholesterolemia and coronary disease. Hypertension was associated with CAD and systolic blood pressure with microalbuminuria. However, these factors could only be considered risk factors in a longitudinal study. Since diabetes is an independent cardiovascular risk factor, the frequent aggregation of other risk factors increases considerably the morbidity and mortality of diabetic patients, emphasizing the importance of the adoption of aggressive therapeutic measures toward glycemic, lipid and arterial pressure control during primary and secondary prevention.

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