LOW HDL-CHOLESTEROL: A COMPONENT OF THE METABOLIC SYNDROME ONLY IN THE PRESENCE OF FASTING HYPERTRIGLYCERIDEMIA IN TYPE 2 DIABETIC PATIENTS

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SUMMARY - The relation between isolated low HDL-cholesterol and the components of the metabolic syndrome is poorly known in type 2 diabetes. We evaluated cardiovascular risk parameters in type 2 diabetic patients with low HDL-cholesterol, compared to those with low HDL-cholesterol and hypertriglyceridemia, isolated hypertriglyceridemia and normal lipid parameters. Patients with low HDL-cholesterol/high triglycerides had higher BMI (29.6 ± 5.7 vs 27.9 ± 4.4 or vs 28.1 ± 5.2 kg/m²), prevalence of obesity (69% vs 55% or vs 54%), higher levels of uric acid (339.0 ± 83.3 vs 303.3 ± 95.2 or vs 303.3 ± 89.2 µmol/l) and C-peptide (0.76 ± 0.40 vs 0.63 ± 0.33 or vs 0.63 ± 0.36 nmol/l) and number of components of the metabolic syndrome (27% patients with all the components) compared to patients with isolated low HDL-cholesterol or normal subjects, respectively. A similar pattern of values was evident in patients with isolated hypertriglyceridemia. With logistic regression analysis, BMI and uric acid levels were significantly associated with the presence of hypertriglyceridemia (both isolated or associated with low HDL-cholesterol), while patients with isolated low HDL-cholesterol and those without dyslipidemia displayed a similar more favourable metabolic pattern. These results indicate that low HDL-cholesterol is a component of the metabolic syndrome only in the presence of fasting hypertriglyceridemia in type 2 diabetic patients.

Key-words: isolated low HDL-cholesterol, metabolic syndrome, fasting hypertriglyceridemia.

RÉSUMÉ - Diminution du cholestérol-HDL : une composante du syndrome plurimétabolique seulement retrouvée en présence d’une hypertriglycéridémie à jeun chez le diabétique de type 2.

La relation entre la baisse isolée du cholestérol-HDL et les composants du syndrome plurimétabolique au cours du diabète de type 2 est mal connue. Nous avons évalué les facteurs de risque cardiovasculaire chez des diabétiques de type 2 avec cholestérol-HDL bas, par comparaison avec les patients avec cholestérol-HDL bas et hypertriglycéridémie, avec hypertriglycéridémie isolée, et avec profil lipidique normal. Les patients avec cholestérol-HDL bas/triglycérides élevés avaient un BMI plus fort (29.6 ± 5.7 vs 27.9 ± 4.4 ou vs 28.1 ± 5.2 kg/m²), une prévalence de l’obésité plus élevée (69 % vs 55 % ou vs 54 %), de plus forts niveaux d’acide urique (339,0 ± 83,3 vs 303,3 ± 95,2 ou vs 303,3 ± 89,2 µmol/l) et de C-peptide (0,76 ± 0,40 vs 0,63 ± 0,33 ou vs 0,63 ± 0,36 nmol/l) et de composants du syndrome plurimétabolique (27 % des patients avec tous les composants), par rapport aux patients avec cholestérol-HDL bas isolé et aux sujets normaux, respectivement. Un profil similaire était retrouvé chez les patients avec hypertriglycéridémie isolée. En analyse de régression logistique, le BMI et l’acide urique étaient significativement liés avec la présence d’une hypertriglycéridémie isolée ou associée avec un cholestérol-HDL bas, tandis que les patients avec cholestérol-HDL bas isolé et ceux avec dyslipidémie présentaient un profil métabolique plus favorable. Ces résultats montrent que le cholestérol-HDL bas est un composant du syndrome plurimétabolique seulement en présence d’une hypertriglycéridémie à jeun chez les diabétiques de type 2.

Mots-clés : cholestérol-HDL bas isolé, syndrome métabolique, hypertriglycéridémie à jeun.
PATIENTS AND METHODS

All 2113 patients with type 2 diabetes, referring to the Diabetic Clinic of Asti (a town of Northern Italy), were evaluated. Data were collected from August 1996 to September 1997. These patients represent the 1.6 % of the reference population (134464 subjects). As the prevalence of known type 2 diabetes is 2 % in 1996 to September 1997. These patients represent the study compares cardiovascular risk parameters in type 2 diabetic patients with isolated low HDL-cholesterol, isolated hypertriglyceridemia, and low HDL-cholesterol combined with hypertriglyceridemia.

Definitions

Patients treated with fibrates or statins (10.6 %) were excluded.

BMI was calculated as weight in kilograms divided by the square of the height in meters. Blood pressure was reported as the average of the last three determinations. Hypertension was defined as a systolic or diastolic blood pressure of 140/90 mmHg or higher, and/or a current antihypertensive treatment.

Cigarette smoking habits were classified in three levels: non-smoker (subjects who had never smoked), ex-smoker (subjects who had quit smoking at least one month earlier), and smoker (current smokers, any amount).

Hypertension was defined as a systolic or diastolic blood pressure ≥ 140/90 mmHg, as the average of the last three determinations and/or a current antihypertensive treatment.

Normal fasting triglycerides (< 1.7 mmol/l) and cholesterol (< 5.2 mmol/l), and low HDL-cholesterol (< 0.9 mmol/l in males and < 1.15 mmol/l in females) were defined in accordance to the targets of good control, proposed by the European Consensus. Overweight/obesity were defined in accordance with these targets as a BMI ≥ 27 kg/m² for males or > 26 kg/m² for females. Microalbuminuria was defined as an albumin excretion rate (AER) of 20-200 µg/min and macroalbuminuria as an AER higher than 200 µg/min at least in two of three urine collections within 6 months (immunoturbidimetric method). Impaired renal function was defined if macroalbuminuria and/or creatinin values > 107 µmol/l in males and > 91 µmol/l in females were present.
The study population was divided into four lipid phenotypes. Patients with isolated low HDL-cholesterol (group 1); patients with low HDL-cholesterol/high triglycerides (group 2); patients with isolated hypertriglyceridemia (group 3) and patients without dyslipidemia (group 4). Therefore, 869 patients were analyzed, while 1019 subjects with total cholesterol ≥ 5.2 mmol/l were excluded. No significant difference was evident between the four lipid phenotypes in smoking habits, alcohol intake and exercise levels. Hyperuricemia was defined as a value of uric acid >345 µmol/l. Informed consent was obtained by all patients. Five women were using oestrogen therapy (2 in group 3 and 1 in each of the other groups).

Analysis of variance or the chi-square test were used to compare means for continuous variables or frequencies for discrete variables. Comparisons of BMI, blood pressure, HbA1c, uric acid and C-peptide levels were carried out by ANOVA/MANOVA, adjusting for age, sex and duration of diabetes. Multiple logistic regression analysis based on the maximum-likelihood method was performed to evaluate the association between each lipid phenotype and BMI, C-peptide and uric acid levels. Since C-peptide and AER levels were not normally distributed, they were log-transformed.

RESULTS

Table I and II show the lipid and clinical characteristics of the patients according to the four lipid phenotypes. Group 1 and group 4 patients had lower levels of BMI, uric acid and C-peptide and lower prevalence of overweight/obesity, if compared to group 2 and group 3. Group 4 patients were significantly older and had a longer duration of diabetes. No significant difference was evident between the four groups for values of albumin excretion rate and prevalence of microalbuminuria, macroalbuminuria and impaired renal function. The components of the metabolic syndrome (obesity, hypertension and hyperuricemia) were evaluated in each lipid phenotype: groups 1 and 4 had a significantly lower prevalence of patients with all the components and a higher prevalence of patients without any component compared to the other two groups.

In a logistic regression model, only BMI remained negatively associated with isolated low HDL-cholesterol, while values of BMI, C-peptide and uric acid correlated with low HDL-cholesterol/high triglycerides and isolated hypertriglyceridemia, after adjustment for sex, age and duration of diabetes.

### Table I. Lipid phenotype and clinical characteristics of type 2 diabetic patients.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>168</td>
<td>102</td>
<td>107</td>
<td>492</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.7 ± 11.5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>65.7 ± 13.2</td>
<td>63.2 ± 12.6</td>
<td>66.9 ± 11.4&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex males/females (%)</td>
<td>51/49</td>
<td>43/57&lt;sup&gt;h&lt;/sup&gt;</td>
<td>57/43</td>
<td>56/44&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>Known duration of diabetes (yr)</td>
<td>9.2 ± 7.5&lt;sup&gt;i&lt;/sup&gt; (1-40)</td>
<td>8.2 ± 7.4&lt;sup&gt;e&lt;/sup&gt; (1-36)</td>
<td>7.6 ± 6.9&lt;sup&gt;e&lt;/sup&gt; (1-37)</td>
<td>11.1 ± 8.1 (1-46)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.9 ± 4.4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>29.6 ± 5.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29.9 ± 6.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28.1 ± 5.2&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.4 ± 0.7</td>
<td>4.4 ± 0.5</td>
<td>4.5 ± 0.5</td>
<td>4.4 ± 0.6</td>
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<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>0.8 ± 0.1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.8 ± 0.2&lt;sup&gt;d, e&lt;/sup&gt;</td>
<td>1.1 ± 0.2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.3 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.1 ± 0.3&lt;sup&gt;c, o&lt;/sup&gt;</td>
<td>2.3 ± 0.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.1 ± 0.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.0 ± 0.3&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diet alone (%)</td>
<td>13.1</td>
<td>12.7</td>
<td>11.2</td>
<td>15.2</td>
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<tr>
<td>Metformin alone (%)</td>
<td>1.2</td>
<td>1.0</td>
<td>1.9</td>
<td>0.4</td>
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<tr>
<td>Sulfonylurea alone (%)</td>
<td>28.6</td>
<td>33.3</td>
<td>33.6</td>
<td>30.3</td>
</tr>
<tr>
<td>Metformin + Sulfonylurea (%)</td>
<td>22.6</td>
<td>21.6</td>
<td>28</td>
<td>24.4</td>
</tr>
<tr>
<td>Insulin (%)</td>
<td>34.5</td>
<td>31.4</td>
<td>25.2</td>
<td>29.7</td>
</tr>
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</table>

Mean ± SD : between ( ) : minimum and maximum duration of diabetes ; Group 1 = isolated low HDL-cholesterol ; group 2 = low HDL-cholesterol/high triglycerides ; group 3 = isolated high triglycerides ; group 4 = normals. <sup>b</sup> p < 0.01 vs group 1 ; <sup>c</sup> p < 0.01 vs group 2 ; <sup>d</sup> p < 0.01 vs group 3 ; <sup>o</sup> p < 0.01 vs group 4 ; <sup>p</sup> < 0.05 vs group 1 ; <sup>q</sup> p < 0.05 vs group 2 ; <sup>r</sup> p < 0.05 vs group 3 ; <sup>t</sup> p < 0.05 vs group 4.
DISCUSSION

BMI, uric acid levels and the number of components of the metabolic syndrome were significantly higher in the presence of hypertriglyceridemia (both isolated or associated with low HDL-cholesterol). Patients with isolated low HDL-cholesterol and those without dyslipidemia displayed a similar pattern of cardiovascular risk factors, that was less severe than that of hypertriglyceridemic patients. Our results are consistent with two previous reports [4, 6], but disagree with another one [5]. However any comparison between these results and ours is difficult due to many differences in the study design: general population instead of diabetic patients, different ethnic groups, lower age and a different cut-off level for triglycerides.

Laakso et al. [11] found that HDL-cholesterol is associated with insulin resistance in all subjects, except in those with type 2 diabetes. It must be stressed, however, that these authors did not consider subjects with isolated low HDL-cholesterol as a separate group.

As many components of the metabolic syndrome cluster only in the presence of hypertriglyceridemia, it seems more appropriate to consider only triglyceride values in the definition of dyslipidaemia in the metabolic syndrome, at least in type 2 diabetic patients.

REFERENCES

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