Type 2 diabetes without the atherogenic metabolic triad does not predict angiographically-assessed coronary artery disease in women

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Running title: Diabetes and coronary artery disease in women

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Evidence suggests that the CHD risk of type 2 diabetes is heterogeneous and that it is affected by the presence/absence of the metabolic syndrome(1). We have previously reported that specific features of the metabolic syndrome (atherogenic metabolic triad) was associated with a 20-fold increase in the risk of developing CHD(2). Considering the costs and lack of standardization of these indices in clinical practice, we have also suggested that the simultaneous measurement and interpretation of waist circumference and fasting TG levels was useful to identify individuals with the atherogenic metabolic triad and at increased CAD risk(3). The main objective of the present study was to compare the risk of CAD between non-diabetic and type 2 diabetic women with/without features of the atherogenic metabolic triad.

RESEARCH DESIGN AND METHODS

This cross-sectional study was conducted in a sample of 250 women (56.2±9.1 years) who underwent an angiographic procedure for the investigation of retrosternal pain. Subjects were French Canadians of European origin (Caucasians). Inform written consent was obtained and the study approved by the Chicoutimi Hospital Ethics Committee. Coronary angiographic disease was assessed by angiography(4). Anthropometric measurements were performed following standardized techniques(5). Fasting lipid profile, glycemia and LDL particle size(6-8) were determined according to routine methods. The HOMA model was used to estimate insulin resistance (fasting insulinXfasting glucose)/22.5(9). Non-diabetic and diabetic women were classified according to previously established diagnosis of type 2 diabetes or by their fasting glucose concentrations (≥7.0 mmol/L). Non-diabetic women without CAD and with a BMI<25 kg/m² (n=25) were used to arbitrarily determine the reference value for apolipoprotein B using the 50th percentile of the variable (0.85 g/L). Cutoffs for insulin levels and LDL particle size corresponded to 60 pmol/L and 255 Å determined from published studies(10; 11). Specificity and sensitivity analyses were performed to determine TG and waist girth cutoffs associated with the absence/presence of the atherogenic metabolic triad. A plasma TG cutoff of 1.6 mmol/L combined with a waist circumference of 85 cm gave optimal sensitivity and specificity (66% for both). To keep our algorithm simple for physicians, values of 1.5 mmol/L and 85 cm were selected.

Group differences for continuous variables were examined using Student unpaired t-tests or by ANOVA. Fasting TG levels were log-transformed. Logistic regression models were used for modeling risk relations considering age, menopausal status, smoking habits and hormone replacement therapy as possible confounders. Women were classified into two or three groups according to their diabetic status and the presence/absence of the atherogenic metabolic triad. The non-diabetic group or the non-diabetic group characterized by 0 to 1 feature of the atherogenic metabolic triad were considered as reference groups. Comparison of prevalence data among subgroups was performed by the likelihood χ² analysis. Analyses were performed with the SAS software.

RESULTS

The odds ratio (OR) of being affected by CAD was increased by 3.8-
fold (95% CI:1.5-9.2;p<0.004) among type 2 diabetic women compared to non-diabetic women. This association remained significant even after adjustment for confounding variables (OR:3.3, 95% CI:1.0-10.0;p=0.04). However, CAD risk in women with type 2 diabetes was only significantly increased among those showing 2-3 features of the atherogenic metabolic triad (OR:8.0, 95% CI:1.8-34.9;p<0.006), whereas diabetes per se was not predictive of CAD in the absence of the atherogenic metabolic triad (0-1 feature). Adjustment for confounders attenuated this relationship which nevertheless remained significant (OR:4.7, 95% CI:1.0-22.1;p<0.05).

An increased proportion (71%) of type 2 diabetic women with 2-3 features of the atherogenic metabolic triad were characterized by hypertriglyceridemic waist (waist circumference≥85 cm and fasting TG levels≥1.5 mmol/L), whereas in the absence of the atherogenic metabolic triad (0-1 feature), its prevalence only reached 43% in type 2 diabetic women and 31% in non-diabetic women.

Characteristics of non-diabetic and type 2 diabetic women with/without CAD are shown in the Table. Type 2 diabetic women with CAD were characterized by a more disturbed fasting plasma lipoprotein-lipid profile compared to type 2 diabetic women without CAD. Among type 2 diabetic women, 68% with CAD had hypertriglyceridemic waist whereas none of CAD negative had this phenotype.

CONCLUSIONS

Using NHANES III data, Alexander et al.(1) found that when compared to diabetic patients with the metabolic syndrome, diabetic patients without the metabolic syndrome (using NCEP-ATPIII criteria(12)) showed a reduced prevalence of CHD(1). These results provided evidence that diabetes is a heterogeneous condition and that diabetic subjects characterized by the metabolic syndrome were at substantially increased risk of CHD. Results of the present study are concordant with these previous results and suggest that physicians may need to go beyond glycemia to properly evaluate/manage CAD risk in their patients with type 2 diabetes.

We have previously suggested that fasting insulin concentrations, apolipoprotein B levels and LDL size could improve our ability to identify high-risk patients (2). We recognize, however, that these markers are not widely available in clinical practice. Therefore, we had suggested that the simultaneous measurement and interpretation of waist circumference and fasting TG levels could help identify high risk subjects with the atherogenic metabolic triad (3; 13-16). Seventy-one percent of type 2 diabetic women with hypertriglyceridemic waist were characterized by 2-3 features of the atherogenic metabolic triad, underlining the importance of this phenotype in the initial screening of high-risk CAD patients even among women with type 2 diabetes.

In the present study, type 2 diabetes was diagnosed using fasting glucose concentrations. Unfortunately, we did not have access to the 2-hour glucose criterion which would have improved the identification of diabetic subjects. Therefore, we acknowledge that the diagnosis of diabetes was probably underestimated. In addition, the number of type 2 diabetic women without CAD was rather small, increasing the probability of a type 2 error (false negative). Thus,
results of this angiographic study suggest that diabetes per se is not predictive of CAD in women in the absence of features of the metabolic syndrome. These results provide further support to the notion that abdominal obesity and hypertriglyceridemia as markers of the metabolic syndrome are important CAD risk factors to assess/manage in women with type 2 diabetes.

ACKNOWLEDGMENTS

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REFERENCES

**TABLE**

Physical characteristics and fasting metabolic profile of non-diabetic and diabetic women stratified on the basis of their coronary artery disease status

<table>
<thead>
<tr>
<th></th>
<th>Non-diabetic women</th>
<th>Diabetic women</th>
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<tbody>
<tr>
<td></td>
<td>CAD(-)</td>
<td>CAD(+)</td>
</tr>
<tr>
<td></td>
<td>n=57</td>
<td>n=134</td>
</tr>
<tr>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>54.8 ± 9.4</td>
<td>55.7 ± 8.9</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>26.1 ± 4.8</td>
<td>26.1 ± 4.8</td>
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<tr>
<td><strong>Waist circumference (cm)</strong></td>
<td>84.6 ± 10.7</td>
<td>85.1 ± 11.7</td>
</tr>
<tr>
<td><strong>Cholesterol (mmol/L)</strong></td>
<td>5.92 ± 1.12</td>
<td>5.88 ± 1.48</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/L)</strong></td>
<td>1.79 ± 0.95</td>
<td>2.39 ± 1.69</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mmol/L)</strong></td>
<td>3.76 ± 1.12</td>
<td>3.49 ± 1.17</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/L)</strong></td>
<td>1.30 ± 0.43</td>
<td>1.20 ± 0.37</td>
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<tr>
<td>Cholesterol/HDL cholesterol</td>
<td>4.96 ± 1.78</td>
<td>5.57 ± 2.41</td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>0.81 ± 0.30</td>
<td>0.79 ± 0.28</td>
</tr>
<tr>
<td>LDL peak particle size (Å)</td>
<td>260.0 ± 3.8</td>
<td>258.5 ± 4.9</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>95.6 ± 50.2</td>
<td>100.5 ± 64.7</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.06 ± 0.59</td>
<td>5.25 ± 0.61</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>21.9 ± 13.4</td>
<td>23.9 ± 17.2</td>
</tr>
<tr>
<td>Prevalence of the hyperTG-waist</td>
<td>32 %</td>
<td>37 %</td>
</tr>
</tbody>
</table>

HyperTG-waist: hypertriglyceridemic waist. The significant difference with the corresponding subgroup is indicated as follows: *: different from subgroup #1; †: different from subgroup #2; ‡: different from subgroup #3 (p<0.04).