Hypertriglyceridemic Waist
A Marker of the Atherogenic Metabolic Triad (Hyperinsulinemia; Hyperapolipoprotein B; Small, Dense LDL) in Men?

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Background—The present study tested the hypothesis that simple variables, such as waist circumference and fasting plasma triglyceride (TG) concentrations, could be used as screening tools for the identification of men characterized by a metabolic triad of nontraditional risk factors (elevated insulin and apolipoprotein [apo] B and small, dense LDL particles).

Methods and Results—Results of the metabolic study (study 1) conducted on 185 healthy men indicate that a large proportion (>80%) of men with waist circumference values ≥90 cm and with elevated TG levels (≥2.0 mmol/L) were characterized by the atherogenic metabolic triad. Validation of the model in an angiographic study (study 2) on a sample of 287 men with and without coronary artery disease (CAD) revealed that only men with both elevated waist and TG levels were at increased risk of CAD (odds ratio of 3.6, P<0.03) compared with men with low waist and TG levels.

Conclusions—It is suggested that the simultaneous measurement and interpretation of waist circumference and fasting TG could be used as inexpensive screening tools to identify men characterized by the atherogenic metabolic triad (hyperinsulinemia, elevated apo B, small, dense LDL) and at high risk for CAD. (Circulation. 2000;102:179-184.)

Key Words: apolipoproteins • insulin • lipoproteins • lipids • coronary disease • waist circumference

There is increasing evidence that variables other than the traditional lipoprotein-lipid profile may further improve the discrimination of individuals at high risk for coronary heart disease (CHD). In this regard, it has been suggested that apolipoprotein (apo) B concentration could be an important predictor of CHD risk. In addition, fasting hyperinsulinemia, used in non-diabetic subjects as a crude marker of insulin resistance, may be a relevant correlate of metabolic abnormalities exacerbating CHD risk in men. Furthermore, small, dense LDL particles have been reported to be more prevalent in CHD patients than in healthy control subjects.

Although recent analyses of the prospective Quebec Cardiovascular Study have shown that the lipid triad (elevated plasma LDL cholesterol and triglyceride [TG] levels and reduced HDL cholesterol) was associated with a substantial increase in the 5-year risk of CHD, we found that hyperinsulinemia, hyperapolipoprotein B (hyperapo B), and small, dense LDL were even more powerful tools to predict CHD in men when these variables were considered simultaneously. We have therefore suggested that this triad of “unconventional” metabolic risk variables (metabolic triad) could be a powerful predictor of CHD risk.

In this regard, we have also shown that this atherogenic metabolic triad is highly prevalent among abdominally obese men, especially when a high accumulation of visceral adipose tissue is present. However, the costs associated with the measurement of visceral adipose tissue accumulation and with the measurement of insulin, apo B, and LDL particle diameter represent major barriers to their widespread use in clinical practice. Because we had previously reported that the waist circumference was a good crude correlate of visceral adipose tissue and of related metabolic complications and because fasting TG concentration has been shown to be the best predictor of LDL size assessed by gradient gel electrophoresis, we tested in 2 different samples the ability of these 2 simple measurements (waist circumference and fasting TG) to (1) identify men with the atherogenic triad of “unconventional” risk variables and (2) predict coronary artery disease (CAD) assessed by angiography.

Methods

Subjects

Metabolic Study Sample (Study 1)
One hundred eighty-five men were recruited from the Quebec City metropolitan area by solicitation through the media. All subjects were sedentary but healthy nonsmoking volunteers and were not under treatment for CHD, diabetes, dyslipidemias, or endocrine

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disorders. Blood samples were drawn after a 12-hour overnight fast. Plasma TG\textsuperscript{13} and cholesterol\textsuperscript{12} concentrations in the plasma and in the lipoprotein subfractions were measured with a Technicon RA-500 analyzer (Bayer Corp). Plasma VLDLs (d<1.006 g/L) were isolated by ultracentrifugation,\textsuperscript{13} and the HDL fraction was obtained after precipitation of LDL in the infranatant (d>1.006 g/L) with heparin and MnCl\textsubscript{4}.\textsuperscript{13} Apo B concentrations were measured in the fasting plasma by the rocket immunoelectrophoretic method of Laurell\textsuperscript{15} as previously described.\textsuperscript{14} LDL peak particle diameter was measured by onedimensioning 2% to 15% polyacrylamide gel electrophoresis of whole plasma as previously described.\textsuperscript{10} Fasting plasma insulin was measured by radioimmunoassay with polyethylene glycol separation.\textsuperscript{17} Body weight, height, and waist circumference were measured by standardized procedures.\textsuperscript{18} Abdominal adipose tissue areas were measured by CT with a Siemens Somatom DHR scanner as previously described.\textsuperscript{19} All participants signed an informed consent document approved by the Laval University Medical Ethics Committee.

**Angiographic Study Sample (Study 2)**

This study sample included unrelated adults who underwent an angiographic procedure for the investigation of retrosternal pain at the Saguenay–Lac-St-Jean regional hospital in Chicoutimi. Patients with type 2 diabetes as well as those known to be affected by familial hypercholesterolemia, type III dyslipidemia, or partial lipoprotein lipase deficiency were excluded. Coronary angiographic disease was assessed by angiography according to previously published procedures.\textsuperscript{20,21} Briefly, 4 coronary arteries were considered for the assessment of coronary stenosis: left main coronary, left anterior descending, circumflex, and right coronary. Patients with ≥1 lesion leading to a minimum 50% lumen narrowing of any of these 4 coronary arterial segments were included in the CAD (+) group. Patients not fulfilling this criterion were classified in the CAD (−) group. Blood samples were obtained in the morning after a 12-hour fast. Plasma total cholesterol, TG, and HDL cholesterol levels were measured by enzymatic assays.\textsuperscript{14,22,23} Total cholesterol was determined in plasma, and HDL cholesterol was measured in the supernatant after precipitation of VLDL and LDL with dextran sulfate and magnesium chloride.\textsuperscript{23} Plasma LDL cholesterol levels were estimated with the Friedewald formula\textsuperscript{24} when TG concentrations were <5.0 mmol/L. Plasma apo B levels were measured according to the rocket immunoelectrophoretic method of Laurell.\textsuperscript{15} Fasting insulinemia was measured by radioimmunoassay with polyethylene glycol separation.\textsuperscript{17} Body weight, height, and waist girth were assessed according to the procedures recommended by the Airlie Conference.\textsuperscript{18} Patients gave their written consent to participate in the study, which was approved by the Chicoutimi Hospital Ethics Committee.

**Statistical Analyses**

Comparisons among subgroups of men classified on the basis of waist and fasting TG values were performed by either Student’s unpaired t test or ANOVA with the general linear model, and the Duncan post hoc test was used when a significant group effect was observed.

**Metabolic Study (Study 1)**

The prevalence of men with the metabolic triad was compared among various subgroups stratified on the basis of waist circumference and TG concentrations. Comparison of prevalence data among subgroups was performed by χ\textsuperscript{2} analysis. Pearson correlation coefficients were computed to quantify the relationships among various variables. All statistical analyses were conducted with SAS software (SAS Institute).

**Angiographic Study (Study 2)**

Multiple logistic regression models were used for modeling relationships between waist girth and triglyceridemia and CAD. Patients were divided into 4 groups according to waist girth (<90 cm or ≥90 cm) and TG levels (<2.0 mmol/L or ≥2.0 mmol/L), and the group characterized by both low waist circumference and low TG concentration was considered the reference group, to which a CAD odds ratio of 1.0 was assigned for comparison purposes. Analyses were carried out with the SPSS package (release 6.1, SPSS Inc).

### Results

All nonobese volunteers (n=38) of the metabolic study (study 1) with body mass index values <25 kg/m\textsuperscript{2} were used to arbitrarily determine, by use of the 50th percentile of variables, reference values for the metabolic triad (high apo B and insulin levels and small, dense LDL particles) (Table 1). The 50th percentile values in nonobese men for fasting insulin, apo B, and LDL peak particle diameter corresponded to 48.5 pmol/L, 0.96 g/L, and 255.5 Å, respectively. Among these nonobese men, 21% were characterized by the metabolic triad.

To examine the relationship of waist circumference to the features of the metabolic triad, the entire cohort of the metabolic study (study 1) was divided into deciles of waist girth. Figure 1A shows that apo B concentrations increased rapidly to ~100 cm of waist circumference and then remained stable among higher deciles of waist girth. Fasting insulin levels, conversely, increased progressively as a function increasing waist girth (Figure 1B).

As expected from numerous studies,\textsuperscript{6,10,25} a highly significant correlation was noted between the LDL peak particle diameter determined by gradient gel electrophoresis and fasting TG concentrations (r=−0.56, P<0.0001). Figure 1C presents LDL peak particle diameter values among deciles of fasting TG levels. It appears that most of the reduction in LDL peak particle size was observed at a value somewhere between 1.82 and 2.11 mmol/L. According to our previous analyses, which suggested that a TG value of 1.9 mmol/L was associated with the best sensitivity/specificity to detect the small, dense LDL phenotype from TG levels,\textsuperscript{10} these results suggested that a TG concentration of ~2.0 mmol/L may be a useful and easy-to-remember reference value to screen for the small, dense LDL phenotype.

**Specificity (percentage of adequately classified subjects without the new atherogenic metabolic triad)** and sensitivity

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean±SD</th>
<th>50th Percentile Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43.1±8.2</td>
<td>48.5</td>
</tr>
<tr>
<td>Body mass index, kg/m\textsuperscript{2}</td>
<td>23.5±1.7</td>
<td></td>
</tr>
<tr>
<td>Waist, cm</td>
<td>84.3±6.7</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.42±0.88</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.78±0.84</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.10±0.79</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.07±0.23</td>
<td></td>
</tr>
<tr>
<td>Cholesterol/HDL cholesterol</td>
<td>4.74±1.57</td>
<td></td>
</tr>
<tr>
<td>Insulin,* pmol/L</td>
<td>49.2±23.5</td>
<td></td>
</tr>
<tr>
<td>Apo B,* g/L</td>
<td>0.98±0.22</td>
<td>0.96</td>
</tr>
<tr>
<td>LDL diameter,* Å</td>
<td>254.2±5.4</td>
<td>255.5</td>
</tr>
<tr>
<td>Visceral adipose tissue, cm\textsuperscript{2}</td>
<td>99.8±42.4</td>
<td></td>
</tr>
</tbody>
</table>

*This sample was used to determine the 50th percentile values for the 3 new risk variables* proposed as the "metabolic triad."
Analyses were performed to verify whether our TG and waist girth cutoff points were appropriate. Plasma TG cutoff points of 1.9 or 2.0 mmol/L, combined with a waist circumference of 85 or 90 cm, corresponded to values at which both optimal sensitivity (73% to 78%) and specificity (78% to 81%) were obtained (results not shown). To keep our algorithm as simple as possible for clinicians, we selected values of 2.0 mmol/L for TG and 90 cm for waist girth as critical cutoff points to screen for the nontraditional metabolic triad. Figure 2 illustrates the working model we used, in which the waist circumference was considered a proxy variable for apo B and fasting insulin levels, whereas TG concentrations were used to screen for the presence of small, dense LDL particles.

Figure 1. Average apo B (A) and fasting insulin (B) levels among deciles of waist circumference. Number within each bar is mean waist girth for each decile. C, Average LDL peak particle diameter among deciles of TG concentrations. Number within each bar is average TG concentration for each decile. Number above bars indicates significant difference from corresponding decile (P<0.05). Dotted line identifies mean apo B, fasting insulin, and LDL peak particle diameter of overall cohort of 185 men for A, B, and C, respectively.

The frequency of men characterized by the atherogenic metabolic triad in each subgroup of waist girth and TG levels is presented in Figure 3. The subgroup of men having small waist girth values (<90 cm) and elevated TG levels (≥2.0 mmol/L) was not included in the analyses because too few such men (n=5) were found for meaningful comparisons. Figure 3 shows that a high proportion of men with waist circumference values ≥90 cm and with elevated TG concentrations (>80%) were characterized by the atherogenic metabolic triad, irrespective of whether they had a moderately elevated (≥90 cm but <100 cm) or a substantially increased (≥100 cm) waist circumference. However, moderately or substantially elevated waist circumferences alone (≥90 cm but <100 cm and ≥100 cm) in the absence of TG≥2.0 mmol/L were not enough to adequately discriminate men with the metabolic triad (only 12% and 53% of men had the triad for moderately and substantially elevated waist girths, respectively). Thus, the simultaneous presence of an
TABLE 2. Plasma Insulin and Apo B Concentrations and LDL Peak Particle Diameter Among Men of the Metabolic Study (Study 1) Stratified on the Basis of Waist Circumference and TG Levels

<table>
<thead>
<tr>
<th>Group (Waist Circumference; TG)</th>
<th>A (&lt;90 cm; &lt;2 mmol/L)</th>
<th>B (90–100 cm; &lt;2 mmol/L)</th>
<th>C (90–100 cm; ≥2 mmol/L)</th>
<th>D (&gt;100 cm; &lt;2 mmol/L)</th>
<th>E (&gt;100 cm; ≥2 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>40</td>
<td>25</td>
<td>30</td>
<td>34</td>
<td>61</td>
</tr>
<tr>
<td>Age, y</td>
<td>46.8 ± 7.6</td>
<td>49.3 ± 6.7†</td>
<td>50.8 ± 7.4†</td>
<td>54.1 ± 5.5†§</td>
<td>52.3 ± 6.6†</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.5 ± 6.5</td>
<td>28.2 ± 4.2</td>
<td>29.9 ± 7.3</td>
<td>31.8 ± 4.6</td>
<td>29.2 ± 4.1</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>99.9 ± 13.2</td>
<td>98.9 ± 10.1</td>
<td>100.7 ± 12.9</td>
<td>102.5 ± 11.3</td>
<td>101.2 ± 11.7</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.51 ± 2.78</td>
<td>2.69 ± 1.84</td>
<td>3.82 ± 2.78</td>
<td>5.60 ± 1.6</td>
<td>5.22 ± 1.38‡</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>3.82 ± 0.95</td>
<td>4.19 ± 0.99†</td>
<td>3.08 ± 0.95</td>
<td>5.08 ± 0.95</td>
<td>5.22 ± 0.95</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>1.01 ± 0.22</td>
<td>0.86 ± 0.20†</td>
<td>1.12 ± 0.12</td>
<td>2.68 ± 0.12</td>
<td>2.62 ± 0.12</td>
</tr>
<tr>
<td>Cholesterol/HDL cholesterol</td>
<td>6.00 ± 1.76</td>
<td>7.78 ± 3.06†</td>
<td>6.82 ± 1.76†</td>
<td>12.58 ± 1.76</td>
<td>11.27 ± 1.76</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
<td>99.4 ± 80.6</td>
<td>146.8 ± 115.9†</td>
<td>192.8 ± 115.9</td>
<td>295.0 ± 115.9</td>
<td>268.0 ± 115.9</td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>1.07 ± 0.24</td>
<td>1.21 ± 0.25†</td>
<td>1.31 ± 0.25</td>
<td>1.90 ± 0.25</td>
<td>1.70 ± 0.25</td>
</tr>
</tbody>
</table>

*Insulin levels were log₂ transformed. Values are means ± SD.
†Significantly different from group A.
‡Significantly different from group B.
§Significantly different from group C.

TABLE 3. Characteristics of Men Involved in the Angiographic Study (Study 2)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A, CAD(−)</td>
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<tr>
<td>No. of subjects</td>
<td>40</td>
</tr>
<tr>
<td>Age, y</td>
<td>46.8 ± 7.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.5 ± 6.5</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>99.9 ± 13.2</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.51 ± 2.78</td>
</tr>
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<td>Cholesterol, mmol/L</td>
<td>3.82 ± 0.95</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>1.01 ± 0.22</td>
</tr>
<tr>
<td>Cholesterol/HDL cholesterol</td>
<td>6.00 ± 1.76</td>
</tr>
<tr>
<td>Insulin, pmol/L†</td>
<td>99.4 ± 80.6</td>
</tr>
<tr>
<td>Apo B, g/L‡</td>
<td>1.07 ± 0.24</td>
</tr>
</tbody>
</table>

*Significantly different from group A.
†Significantly different from group B.
‡Significantly different from group C.
§Significantly different from group D.

Increased waist circumference and elevated TG concentrations is necessary to substantially increase the likelihood of finding individuals characterized by the metabolic triad.

Characteristics of subgroups classified on the basis of waist girth and TG levels are presented in Table 2. The cholesterol/HDL cholesterol ratio was substantially elevated in subgroups with both a high waist girth and elevated TG values. The cholesterol/HDL cholesterol ratio was also elevated in men presenting a high waist circumference value but low TG concentrations. However, this ratio was 1 unit lower than in the former group characterized by higher fasting insulin concentrations. As expected, LDL peak particle diameter appeared to be largely influenced by TG levels rather than by waist circumference (P < 0.0001). Men with the highest waist circumference values and elevated TG concentrations had similar apo B concentrations and LDL peak particle size than men with medium waist girth and high TG levels, but the former group was characterized by higher fasting insulin levels (P < 0.0001). In the absence of elevated TG levels, men with increased waist circumference had intermediate LDL peak particle diameter and apo B levels but elevated fasting insulin concentrations.

We then performed a validation study by studying the performance of our simple waist-TG algorithm in a sample of male patients who had coronary angiographic procedures for symptoms of CAD (study 2). Characteristics of subjects.
according to CAD status are presented in Table 3. Overall, patients in the CAD(+) group showed a deteriorated lipoprotein-lipid profile compared with patients in the CAD(−) group. Figure 4 presents multiple logistic regression analyses performed to determine the relationships of waist circumference and TG levels to CAD. The relative odds of being affected by CAD were increased significantly, by 3.6-fold (P<0.03), among men with elevated waist circumference and TG concentrations compared with men in the reference group (low waist girth and TG levels).

Discussion

The objective of the present study was to test whether simple variables, such as waist circumference and TG concentrations, could be used as screening tools for the identification of men characterized by a cluster of new metabolic risk variables for CHD, such as hyperinsulinemia and elevated apo B and small, dense LDL particles. In a prospective case-control analysis of men of the Québec Cardiovascular Study, we recently reported that the simultaneous measurement of insulinemia, apo B, and LDL particle diameter could improve our ability to identify men at high risk for CHD beyond the traditional lipid triad (increased TG and LDL cholesterol and reduced HDL cholesterol levels).7

Although there are considerable data linking the traditional lipid triad to CHD risk, we believe that the high risk of CHD noted among men with the metabolic triad of nontraditional risk factors makes sense from a pathophysiological standpoint. However, because most physicians do not have access to these new metabolic markers of CHD risk, there was a need to develop simple and inexpensive screening procedures that could improve the ability of general physicians and other health professionals to identify, at low cost, potential carriers of this atherogenic metabolic triad. Analyses conducted in our study sample 1 revealed that a large proportion of men with intermediate (≥90 but <100 cm) and large (≥100 cm) waist girth values and with TG concentrations >2.0 mmol/L were characterized by the triad of nontraditional metabolic risk factors. They were also characterized by substantial elevations in their cholesterol/HDL cholesterol ratio (a well-accepted predictor of CHD risk)26 and by increased levels of visceral adipose tissue, which were far above our previously suggested critical value (130 cm²).27 Conversely, it is also important to point out that 50% of men with TG levels <2.0 mmol/L but with high waist circumference values (≥100 cm) were characterized by the atherogenic triad; yet, they had very high levels of visceral adipose tissue. Moreover, only 12% of men with an intermediate waist girth (≥90 but <100 cm) but with TG levels <2.0 mmol/L had the atherogenic triad. Results of the angiographic study (study 2) also revealed that only men with elevated waist girth and TG levels were at greater risk for CAD. Thus, results of both our metabolic and angiographic studies suggest that an elevated waist girth is, by itself, not enough to identify men with the atherogenic metabolic triad and that considering the presence of a moderate hypertriglyceridemia (≥2.0 mmol/L) could further improve the screening procedure.

Results from published prospective studies have also shown that apo B is a significant predictor of CHD, although this is not a uniform finding.2,28 In the present study, we found a positive association between apo B levels and waist circumference as apo B concentrations progressively increased with waist girth. We observed a rapid increase in apo B levels up to ≈100 cm of waist circumference. Above this value, a further increase in waist girth was not associated with substantial changes in apo B concentrations. Therefore, it seems that apo B levels are very sensitive to an increase in waist girth resulting from an accumulation of visceral adipose tissue. Analyses on sensitivity and specificity revealed that 90 cm of waist circumference was the critical cutoff point in screening for the nontraditional lipid triad, which included elevated apo B concentrations.

Our previous work has also demonstrated a positive association between waist girth and fasting as well as postglucose insulin levels.9 In our metabolic study (study 1), men with elevated waist girth were also characterized by higher levels of visceral adipose tissue and by elevated fasting insulin concentrations. Thus, in the present cohort of men, fasting insulin levels increased consistently with waist circumference. We have suggested that this hyperinsulinemic state in nondiabetic abdominally obese men was a marker of insulin resistance and a risk factor for CHD,4,21 although this issue is still controversial.

There is also evidence that the small, dense LDL phenotype is quite prevalent among patients with CHD. In the Québec Cardiovascular Study, we reported that the concomitant variation in apo B level was critical in the determination of CHD risk among men with small, dense LDL particles.6 Thus, TG concentrations are the best predictors of the dense LDL phenotype, but the presence of small, dense LDL particles alone may not be sufficient to substantially increase CHD risk. This is therefore why we believe that the measurement of waist girth (as a correlate of elevated insulin and apo B levels), in addition to fasting TG levels, is important in the assessment of CHD risk in men.

In summary, we tested, in 2 independent study samples, the ability of simple and inexpensive tools to screen for high-risk patients. It is suggested that the simultaneous interpretation of waist girth and fasting TG levels may contribute to a better identification of individuals characterized by the simultaneous presence of hyperinsulinemia, hyperapo B, and the small, dense LDL phenotype who are at increased risk of CHD. This “hypertriglyceridemic waist” concept may prove to be a helpful approach for the cost-effective screening of the population.

Acknowledgments

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