The Metabolic Syndrome, LDL Particle Size, and Atherosclerosis

The Atherosclerosis and Insulin Resistance (AIR) Study

Johannes Hulthe, Lena Bokemark, John Wikstrand, Björn Fagerberg

Abstract—An operative definition of the metabolic syndrome has been suggested by a working group associated with the World Health Organization in 1998. The aim of this study was to examine whether small, low density lipoprotein (LDL) particle size was associated with the metabolic syndrome and with subclinical atherosclerosis as measured by ultrasound in the carotid and femoral arteries. The study was performed in a population-based sample of clinically healthy men (N=391), all 58 years old and not undergoing any treatment with cardiovascular drugs. Exclusion criteria were cardiovascular or other clinically overt diseases or continuous medication with cardiovascular drugs. The results showed that subjects characterized by the metabolic syndrome (n=62) had a thicker mean intima-media complex (IMT) in both the carotid and femoral arteries (0.86 versus 0.77 mm, P<0.001, and 1.03 versus 1.00 mm, P=0.022, respectively) and also lower mean values for LDL particle size (25.78 versus 26.80 nm, respectively, P<0.001) compared with subjects with no risk factors (n=77). The group with the metabolic syndrome (n=62) also had higher mean values for serum cholesterol and heart rate. In the whole study group (N=391), there were significant but weak negative relationships between small LDL particle size, increasing IMT, and increasing cross-sectional intima-media area of the carotid and femoral arteries and also negative relationships between LDL particle size and plaque occurrence and size in the carotid and femoral arteries. In summary, this is the first large-scale study to demonstrate a relationship between the clustering of risk factors that constitute the metabolic syndrome and a small LDL particle size pattern and the occurrence of preclinical atherosclerosis in the carotid and femoral arteries, as assessed by the ultrasound technique, in healthy 58-year-old men recruited from the general population. (Arterioscler Thromb Vasc Biol. 2000;20:2140-2147.)

Key Words: metabolic syndrome • atherosclerosis • ultrasound • LDL particle size

The observation that insulin resistance is associated with a clustering of risk factors for cardiovascular disease has led to the suggestion of a syndrome, which has been given different names, eg, the metabolic syndrome or the insulin resistance syndrome.1 However, it is still unclear how this proposed syndrome should be delineated and how the underlying mechanisms affect the cardiovascular disease process.1 Central to the hypothesis is the concept that insulin resistance leads to a multitude of perturbations that in the end may cause atherosclerotic disease.1 Also, other risk markers have been associated with the metabolic syndrome, such as heart rate,2,3 which seem to be associated with increased sympathetic nervous activity in combination with decreased vagal tone. Earlier studies have indicated an association between insulin resistance and variables related to atherosclerotic disease among whites.4–6 However, the definition of the metabolic syndrome has not yet been fully clarified. An operative definition of the metabolic syndrome has been suggested by a working group associated with the World Health Organization in 1998.7 The dyslipidemia associated with insulin resistance is characterized by hypertriglyceridemia and a low concentration of serum HDL cholesterol.8–10 The hepatic synthesis of lipoproteins and the degradation of circulating lipoproteins are, to a large extent, dependent on insulin action.11–13 The size and composition of the lipoproteins may consequently be related to insulin resistance. Hence, it is generally believed that small LDL particle size may be associated with insulin resistance.14–17 However, there are also several reports that have failed to confirm a relationship between LDL particle size and insulin resistance.18,19 Small LDL particle size has also been suggested to be associated with the development of atherosclerosis as measured by coronary angiography,20–23 but again, this is not a consistent finding.24–28 Taken together, available data show that it is still unclear whether small LDL particle size is related to the insulin resistance syndrome and to the atherosclerotic disease process.

A negative relationship between LDL particle size and intima-media thickness (IMT) has been found in a previous study by Skoglund-Andersson et al.29 In that study, only...
TABLE 1.  Anthropometric Data, Blood Pressure, Heart Rate, Serum Lipids and Lipoproteins, and Smoking Habits of Study Participants

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Group 1: Subjects With the Metabolic Syndrome (n=62)</th>
<th>Group 2: Subjects With &gt;1 Risk Factor (n=252)</th>
<th>Group 3: Subjects With No Risk Factors (n=77)</th>
<th>Mean Difference (1-3)</th>
<th>95% CI for Difference (1-3)</th>
<th>P Value for Difference (1-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>30.72±3.35</td>
<td>26.61±4.01</td>
<td>22.30±2.13*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>145±19</td>
<td>136±19</td>
<td>125±12*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>88±11</td>
<td>82±10</td>
<td>75±7*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>70±11</td>
<td>64±10</td>
<td>60±8</td>
<td>10</td>
<td>7 to 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>6.23±1.21</td>
<td>6.02±1.14</td>
<td>5.82±0.88</td>
<td>0.41</td>
<td>0.06 to 0.76</td>
<td>0.030</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>2.46±1.81</td>
<td>1.52±0.75</td>
<td>0.97±0.28*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.14±0.40</td>
<td>1.23±0.31</td>
<td>1.52±0.42*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.04±0.93</td>
<td>4.11±0.99</td>
<td>3.86±0.88</td>
<td>0.18</td>
<td>−0.13 to 0.49</td>
<td>0.211</td>
</tr>
<tr>
<td>Apo A-1, g/L</td>
<td>1.37±0.26</td>
<td>1.41±0.21</td>
<td>1.52±0.24</td>
<td>−0.15</td>
<td>−0.24 to −0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>1.32±0.27</td>
<td>1.23±0.28</td>
<td>1.08±0.22</td>
<td>0.24</td>
<td>0.15 to 0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>6.08±2.43</td>
<td>4.71±0.56</td>
<td>4.61±0.43*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma insulin, mU/L</td>
<td>19.43±9.62</td>
<td>8.83±3.18</td>
<td>6.10±1.52*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present smoker, %</td>
<td>19.4</td>
<td>25.4</td>
<td>23.7</td>
<td>by χ²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past smoker, %</td>
<td>53.2</td>
<td>39.3</td>
<td>28.6</td>
<td>P=0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette-years, n</td>
<td>639±508</td>
<td>516±356</td>
<td>471±466†</td>
<td>168</td>
<td>386 to −50</td>
<td>0.070</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and HR, heart rate.

*Selection criteria not tested for statistical significance.
†Cigarette-years calculated only for present and past smokers.

Taken together, there has been no previous large-scale study investigating the relationship between the metabolic syndrome, LDL particle size, and atherosclerosis in a population-based sample of clinically healthy subjects. Accordingly, the present study was designed with the aim of examining whether small LDL particle size is associated with the metabolic syndrome and with preclinical atherosclerosis, as measured by ultrasound in the carotid and femoral arteries. The study was performed in a population-based sample of clinically healthy men (N=391), all 58 years old and who were not undergoing any treatment with cardiovascular drugs.

Methods

Study Group

The subjects were randomly selected from among 58-year-old men listed in the county council register of Gothenburg, Sweden. Our power calculation indicated that we needed 800 subjects. An invitation letter was sent to 1728 men, of whom 1188 gave a positive reply. After a telephone interview and a screening examination, 314 subjects fulfilled the exclusion criteria, 19 subjects refused to participate in the study, and 37 subjects could not be reached for the telephone interview. Hence, 818 men were finally recruited to the study, and 37 subjects were homozygous for the apoE3 allele were included. Furthermore, subjects with a high body mass index (BMI >32 kg/m²) and plaque occurrence were excluded. In a subsample of subjects (n=36) recruited from the present study, the reproducibility of LDL particle size determination has been studied. In this pilot study, we also showed a negative relationship between plaque occurrence in the carotid artery and small LDL particle size. However, the study only included 36 subjects and did not address the relationships between small LDL particle size and atherosclerosis in the femoral artery or the carotid bulb, the latter of which is possibly a segment more closely related to coronary atherosclerosis than are common carotid IMT and femoral IMT.

Atherosclerosis and Insulin Resistance (AIR) study. To keep the sociocultural components within a limited range, inclusion criteria were 58 years of age, Swedish ancestry, and living in Gothenburg, Sweden. Exclusion criteria were cardiovascular or other clinically overt diseases (eg, malignancy or psychiatric disease) and continuous medication with cardiovascular drugs (ie, antidiabetic, lipid-lowering, antihypertensive, and heart failure drugs or drugs for angina pectoris). Among these 818 included subjects, 38 (5%) were found to have a blood glucose level ≥6.1 mmol/L at the time of screening. However, none of the subjects had overt diabetes mellitus.

In connection with the screening examination, the subjects were divided into quintiles of a BMI/blood glucose score, which allowed immediate stratification and selection for further studies. The following equation was used: BMI/blood glucose score = 46.22 − 1.27(BMI) − 0.84(whole-body glucose). This algorithm was based on a previous study of clinically healthy men of similar age who had undergone a euglycemic hyperinsulinemic clamp examination. The correlation coefficient between the BMI/blood glucose score and observed insulin sensitivity was 0.81. In the present population sample, this score was significantly correlated with insulin sensitivity measured with the euglycemic hyperinsulinemic clamp method, when expressed as insulin-mediated glucose uptake adjusted both for body weight and for fat-free mass (r=0.69, P<0.001) and r=0.59, P<0.001, respectively; n=104). In a score reproducibility study of 60-year-old men obtained from the background population (n=32) examined at an interval of 2 weeks, this parameter showed a coefficient of variation of 3.39% and a correlation coefficient of r=0.99 between the 2 examinations. All subjects in quintiles 1 and 5 and every fifth subject in quintiles 2 through 4 were invited to participate in future cross-sectional and prospective studies of insulin metabolism and ultrasound examinations of the carotid and femoral arteries (N=391). All men received both written and oral information before consenting to participate in the study. The study was approved by the ethics committee at Sahlgrenska University Hospital.

Fasting Glucose and Insulin Resistance

Glucose intolerance was defined as a fasting blood glucose level ≥5.6 mmol/L. Insulin resistance was defined as a fasting plasma insulin level ≥14.86 mU/L. This definition was obtained by using
the euglycemic hyperinsulinemic clamp method to define glucose uptake below the lowest quartile for the population under investigation in a representative sample of 50 subjects from the present study. The plasma insulin level corresponding to the lowest quartile for glucose uptake was calculated and used as a cutoff point when defining insulin resistance. The positive and negative predictive values of this plasma insulin cutoff point were 0.88 and 0.86, respectively, in 52 subjects from the same background population who had undergone a clamp examination and who were not included in the first calculation above.

**Definition of the Metabolic Syndrome**

The definition suggested by a working group consulted by the World Health Organization in 1998 was used. The metabolic syndrome is defined as glucose intolerance and/or insulin resistance together with 2 or more of the following risk factors: (1) raised arterial (systolic/diastolic) pressure \( \geq 160/90 \) mm Hg (either value); (2) raised triglycerides (\( \geq 1.7 \) mmol/L) and/or low HDL cholesterol (\( < 0.9 \) mmol/L); (3) central body obesity (waist-to-hip ratio \( > 0.90 \)) and/or BMI \( \geq 30 \) kg/m\(^2\); and (4) microalbuminuria (urinary albumin excretion rate \( \geq 20 \) \( \mu \)g/min or albumin-to-creatinine ratio \( \geq 20 \) mg/g). In the present study, subjects with a dipslide reading of 1+ were also included in this category, whereas those with a dipslide reading of \( \geq 1+ \) or a urinary excretion rate \( \geq 208 \) \( \mu \)g/min were excluded from this category.

**LDL Particle Size Determination**

**Gradient Gel Electrophoresis**

LDL particle size was assessed on commercially available, non-denaturing 2% to 16% polyacrylamide gradient gels (Alamo Inc) as previously described. For analyses of ultrasound and LDL particle size variables, the study group \((N=391)\) was divided into 3 subgroups: (1) subjects fulfilling the criteria for the metabolic syndrome \((n=62)\); (2) subjects with at least 1 risk factor \((n=252)\); and (3) subjects with no risk factors \((n=77)\). This latter group was used as a reference group for subjects with the metabolic syndrome.

**Measurement Procedure**

The coefficient of variation (same serum run on different gels on different days) for LDL peak particle size was 0.3%, with a correlation coefficient of \( r=0.99 \). To minimize the reading error

**Figure 1.** Subjects fulfilling criteria for the metabolic syndrome, \( 7 \) subjects with \( \geq 1 \) risk factor but not the full syndrome, and subjects with no risk factors and relationships to common carotid artery IMT (upper panel), carotid artery bulb IMT (middle panel), and common carotid artery cross-sectional intima-media area (lower panel). Values are mean \( \pm \) SE.

**Figure 2.** Subjects fulfilling criteria for the metabolic syndrome, \( 7 \) subjects with \( \geq 1 \) risk factor but not the full syndrome, and subjects with no risk factors and relationships to LDL peak particle size (upper panel), the proportion of small particles (\( B\% \), middle panel), and the proportion of IDL particles (IDL\%, lower panel). Values are mean \( \pm \) SE.
Measurements in the common femoral artery were made in a similar way to those in the carotid artery but along a 15-mm-long section proximal to the bifurcation.\textsuperscript{34} An estimate of the mean cross-sectional area of the IMT was calculated for both the carotid and femoral arteries as the difference between the total area inside the adventitia and the lumen area\textsuperscript{35}: $\pi \left[ \text{lumen diameter}_{mean}^2 / 2 \right] - \pi \left[ \text{lumen diameter}_{mean} / 2 \right]^2$.

### Assessment of Plaque Occurrence

The carotid and femoral arteries were scanned both longitudinally and transversely to assess the occurrence of plaques.\textsuperscript{34} A plaque was defined as a distinct area with an IMT >50\% thicker than that of neighboring sites (as judged visually). A semi-quantitative subjective scale was used to grade the size of plaques into the following categories: (1) grade 1, 1 or more small plaques (less than $\sim10$ mm$^2$); (2) grade 2, moderate to large plaques (The differentiation between grades 1 and 2 was made subjectively in most cases, and quantitative measurements were made by the computerized system\textsuperscript{36} only when the correct classification was not obvious to the observer.); and (3) grade 3, plaques producing flow disturbances.\textsuperscript{34} In the present study, no plaque of grade 3 was found in the femoral artery, but 3 subjects had plaques of grade 3 in the carotid artery. Therefore, plaques of grades 2 and 3 were merged into 1 group of moderate to large plaques. This analysis included plaques in the near wall as well as the far wall of the vessel. Analyses of plaques were

### Ultrasound

**IMT, Lumen Diameter, and Cross-Sectional Area**

The ultrasound images were analyzed in an automated, computerized analysis system.\textsuperscript{33} IMT was defined as the distance from the leading edge of the intima-media complex (ie, IMT). Measurements in the common femoral artery were made in a similar way to those in the carotid artery but along a 15-mm-long section proximal to the bifurcation.\textsuperscript{34} A plaque was defined as a distinct area with an IMT >50\% thicker than that of neighboring sites (as judged visually). A semi-quantitative subjective scale was used to grade the size of plaques into the following categories: (1) grade 1, 1 or more small plaques (less than $\sim10$ mm$^2$); (2) grade 2, moderate to large plaques (The differentiation between grades 1 and 2 was made subjectively in most cases, and quantitative measurements were made by the computerized system\textsuperscript{36} only when the correct classification was not obvious to the observer.); and (3) grade 3, plaques producing flow disturbances.\textsuperscript{34} In the present study, no plaque of grade 3 was found in the femoral artery, but 3 subjects had plaques of grade 3 in the carotid artery. Therefore, plaques of grades 2 and 3 were merged into 1 group of moderate to large plaques. This analysis included plaques in the near wall as well as the far wall of the vessel. Analyses of plaques were

### Table 2. LDL Particle Size (Pattern A vs Pattern B) in Relation to Blood Pressure, BMI, Serum Lipids, Plasma Insulin, Blood Glucose, Smoking Habits, IMT, Lumen Diameter, and Plaque Occurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pattern A: &gt;25.5 nm (n=318)</th>
<th>Pattern B: &lt;25.5 nm (n=62)</th>
<th>95% CI for Differences Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m$^2$</td>
<td>26.0±4.3</td>
<td>28.2±4.2</td>
<td>-3.4 to -1.03†</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>134±19</td>
<td>140±19</td>
<td>-11 to -1*</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>81±10</td>
<td>85±9</td>
<td>-7 to -1†</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>64±10</td>
<td>67±10</td>
<td>-6 to -1†</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>5.95±1.07</td>
<td>6.40±1.21</td>
<td>-0.75 to -0.15†</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.29±0.53</td>
<td>2.96±1.74</td>
<td>-2.11 to -1.23†</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.33±0.36</td>
<td>0.99±0.24</td>
<td>0.27 to 0.41†</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.04±0.96</td>
<td>4.18±0.97</td>
<td>-0.41 to 0.14</td>
</tr>
<tr>
<td>Plasma insulin, μU/mL</td>
<td>9.38±6.00</td>
<td>12.69±6.38</td>
<td>-5.06 to -1.57‡</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>4.86±0.89</td>
<td>5.09±2.17</td>
<td>-0.79 to 0.33</td>
</tr>
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</table>

Smoking status

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Never smoked, %</th>
<th>Past smoker, %</th>
<th>Current smoker, %</th>
<th>Cigarette-years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>38.0</td>
<td>38.1</td>
<td>23.9</td>
<td>301.3±383.4</td>
</tr>
</tbody>
</table>

IMT, mm

<table>
<thead>
<tr>
<th>Artery</th>
<th>Pattern A:</th>
<th>Pattern B:</th>
<th>95% CI for Differences Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotis communis</td>
<td>0.80±0.13</td>
<td>0.83±0.14</td>
<td>-0.064 to 0.006</td>
</tr>
<tr>
<td>Carotis bulb</td>
<td>0.98±0.23</td>
<td>1.07±0.37</td>
<td>-0.184 to 0.016</td>
</tr>
<tr>
<td>Femorals communis</td>
<td>1.04±0.44</td>
<td>1.11±0.46</td>
<td>-0.197 to 0.051</td>
</tr>
<tr>
<td>Lumen diameter, mm</td>
<td>6.24±0.62</td>
<td>6.27±0.62</td>
<td>-0.20 to 0.13</td>
</tr>
<tr>
<td>Carotid plaque occurrence, %</td>
<td>59</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Femoral plaque occurrence, %</td>
<td>63</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>


SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and HR, heart rate.

\*P<0.05; †P<0.01; ‡P<0.001.
performed in both the right and left carotid arteries. The largest plaque in either artery was used in the present analysis. Reproducibility studies of a blinded rereading of plaque occurrence in 53 male subjects showed that plaque size was assessed in the same way on both occasions in 95% of the cases.

Results

Prevalence of Risk Factors in the Study Group
No subjects had overt diabetes mellitus. A blood glucose value ≥ 6.1 mmol/L was found in 22 subjects (5.6%). Eighty-one subjects had a fasting blood glucose level ≥ 5.6 mmol/L and/or insulin resistance (20.7%). There were 96 (25%) subjects who had raised systolic and/or diastolic arterial blood pressure; 127 (33%) subjects had raised triglyceride or low HDL levels; 293 (75%) subjects had central obesity or a raised BMI; and 46 (12%) subjects had microalbuminuria. Sixty-two subjects (16%) fulfilled the criteria for the metabolic syndrome according to the definition given above; 252 (64%) subjects had at least 1 risk factor (but not the full syndrome); and 77 (20%) subjects had no risk factors.

Anthropometric Data, Blood Pressure, Heart Rate, Serum Lipids and Lipoproteins, and Smoking Habits in Subjects With the Metabolic Syndrome Compared With Subjects With No Risk Factors
Subjects with the metabolic syndrome had, as expected, higher BMI, blood pressure, serum triglycerides, blood glucose, and plasma insulin and also lower HDL levels compared with subjects with no risk factors (not tested for statistical significance because of the selection criteria; Table 1). Furthermore, subjects with the metabolic syndrome had significantly higher mean values for heart rate, serum total cholesterol, and apo B compared with subjects with no risk factors (Table 1). There were no differences in mean LDL cholesterol concentrations or cigarette-years between the 2 groups.
IMT, Lumen Diameter, Cross-Sectional Area, Plaque Occurrence, and LDL Particle Size in Subjects With the Metabolic Syndrome Compared With Subjects With No Risk Factors

Subjects with the metabolic syndrome had significantly higher mean values for common carotid artery and carotid artery bulb IMT and cross-sectional intima-media area in the carotid artery compared with subjects with no risk factors (Figure 1). Mean value for lumen diameter in the carotid artery was significantly higher in subjects with the metabolic syndrome compared with subjects with no risk factors (6.38±0.67 and 6.01±0.44 mm, respectively, P=0.001). No significant difference in lumen diameter was seen in the femoral artery. Mean values for IMT and cross-sectional intima-media area of the common femoral artery were significantly higher in subjects with the metabolic syndrome compared with subjects with no risk factors (1.03±0.33 versus 1.00±0.57 mm and 32.6±11.6 versus 28.4±12.6 cm², P=0.022 and P=0.006, respectively). There were no significant differences in plaque occurrence and size in the carotid or femoral arteries between the 2 study groups. Furthermore, subjects with the metabolic syndrome had significantly smaller LDL particles and a smaller proportion of IDL particles compared with subjects with no risk factors (Figure 2).

LDL Particle Size in Relation to Metabolic and Ultrasound Variables

Numbers of subjects characterized by pattern B (small, dense LDL particles) and pattern A (large particles) were 62 and 318, respectively. Subjects with pattern B had significantly higher mean values for BMI, systolic and diastolic blood pressures, heart rate, serum cholesterol, triglyceride levels, and plasma insulin and lower HDL levels compared with subjects with pattern A (Table 2). Subjects with pattern B also had a higher prevalence of moderate to large plaques in the carotid artery compared with subjects with pattern A (Table 2). There were no significant differences between the 2 groups in LDL cholesterol, blood glucose, smoking habits, IMT, lumen diameter, or plaque occurrence in the femoral artery (Table 2).

LDL Peak Particle Size in Relation to IMT, Plaque Occurrence, and Cross-Sectional Area

Decreasing LDL peak particle size was significantly associated with increasing IMT of the common carotid artery, the carotid artery bulb, and the common femoral artery (Figure 3). There was a statistically significant association between plaque occurrence and size and the LDL peak particle diameter in both the carotid and femoral arteries (Figure 4). Thus, smaller LDL particle size was associated with the occurrence of moderate to large plaques. LDL particle size was weakly and negatively associated with cross-sectional area in both the carotid and femoral arteries (r=−0.14 and r=−0.16, P=0.008 and P=0.004, respectively).

Discussion

The results of the present study showed that clinically healthy, 58-year old men with a clustering of risk factors typical of the metabolic syndrome had small LDL particles and an increased thickness of the IMT of the common carotid artery, the carotid artery bulb, and the common femoral artery. The mean value for lumen diameter in the carotid artery but not in the femoral artery was higher in the subjects with the metabolic syndrome compared with the subjects with no risk factors. Furthermore, there was also a weak and negative relationship between LDL particle size and IMT of the common carotid artery, the carotid artery bulb, and the common femoral artery.

These results were obtained in a population-representative sample of 58-year-old, white, untreated men who were selected to minimize the effect of confounding factors such as race, sex, age, and treatment with different drugs for cardiovascular disease. A suggested operative definition of the metabolic syndrome was used because there is today no generally established definition of this syndrome.7 This definition was based on the combination of impaired fasting glucose or insulin resistance and the presence of at least 2 of the factors that are characteristics of the metabolic syndrome.7 We modified this algorithm by using fasting plasma insulin as a measure of insulin resistance, after having defined a cutoff limit corresponding to the lowest quartile of insulin-mediated glucose uptake during a hyperinsulinemic euglycemic clamp examination performed in a random sample of the background population. This cutoff point was also validated in an independent sample from the same background population. In patients with established diabetes mellitus, circulat-
ing insulin levels may not reflect low insulin sensitivity, as among nondiabetics, due to insufficiency of the pancreatic β-cells to increase the secretion of insulin.15 However, we did not include any patients with clinically overt diabetes and those with a blood glucose level ≥6.1 mmol/L demonstrated insulin levels >90th percentile.

The components included in this definition of the metabolic syndrome were high blood pressure, general or upper-body obesity, and dyslipidemia with hypertriglyceridemia or low HDL levels, apart from a disturbed glucose and insulin metabolism. These variables were consequently not tested for statistical significance. The group with the metabolic syndrome also had higher mean values for serum cholesterol and apo B as well as a higher heart rate compared with subjects with none of the risk factors constituting the metabolic syndrome. Both an elevated serum cholesterol and high heart rate are recognized risk factors for cardiovascular disease and may thus have contributed to the ultrasound findings indicating more pronounced atherosclerosis in the group with the metabolic syndrome.3,41 The higher heart rate may be associated with an increased sympathetic nervous system activity, perhaps in combination with vagal withdrawal, that is associated with obesity.3

When we used the aforementioned approach to divide the subjects into those with small versus large LDL particles, a consistent picture emerged: ie, subjects with small LDL particles (pattern B) had higher BMI, blood pressure, heart rate, triglycerides, and plasma insulin and also lower HDL cholesterol levels compared with subjects characterized by larger LDL particles (pattern A). In addition, the occurrence and size of plaques in the carotid artery were also associated with small LDL particle size. Subjects with pattern B also had a tendency toward a thicker IMT in the common carotid artery and the carotid artery bulb compared with subjects with pattern A ($P=0.10$; 95% CI, $-0.064$ to $0.006$ and $P=0.10$; 95% CI, $-0.184$ to $0.016$, respectively). This is the first study to examine healthy, unmedicated subjects from the general population who have a clustering of risk factors constituting the metabolic syndrome in a preclinical stage of atherosclerosis development. Our results are in line with the findings from other studies, showing that small LDL particles are related to such components of the metabolic syndrome as insulin resistance, dyslipidemia, and perturbations in glucose metabolism.15–17 The results from the present study also give support to those previous studies that have shown a relationship between small LDL particles and atherosclerotic disease. The ultrasound technique used in the current study allows measurement of atherosclerosis development at an early stage of the disease process, and IMT of the common carotid artery and the carotid artery bulb has also previously been shown to be associated with coronary atherosclerosis. An association between small LDL particle size and angiographically defined coronary artery disease has thus been found in several studies.20–23 Patients with small, dense LDL particles have also been shown to have a 3-fold increased risk of myocardial infarction, independent of age, sex, and relative weight.43 Small LDL particle size has also been suggested to be an additional risk factor for coronary artery disease.23 In other studies, however, no certain relationship has been found between atherosclerotic disease and LDL particle size.24–28 A negative relationship between LDL particle size and IMT of the common carotid artery has recently been shown in subjects who are homozygous for the apoE3 allele.29 However, in that study subjects with a high BMI (>32 kg/m²) and plaque occurrence were excluded. The results are therefore not directly comparable to the results obtained in the present study.

The mechanisms underlying the development of small LDL particles are not fully known. Insulin resistance is associated with an influx of fatty acids from the splanchnic circulation to the liver, causing an increased production of VLDL particles.11–13 The concomitant reduction in lipoprotein lipase action in the peripheral tissues and the liver is believed to lead to the production of small LDL particles. The proposed proatherogenic properties of small LDL particles may relate to their ability to penetrate the arterial wall,44 to bind more easily to arterial proteoglycans,45,46 and thus be more susceptible to oxidation,47 a key event in the atherosclerotic process.

Our interpretation and conclusion of these data are that the clustering of factors that constitute the metabolic syndrome is associated with a small LDL particle size pattern and to atherosclerosis in the carotid and femoral arteries, as assessed by the ultrasound technique. To summarize, this is the first study to demonstrate a relationship between preclinical atherosclerosis, LDL particle size, and the metabolic syndrome in healthy middle-aged men recruited from the general population.

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The Metabolic Syndrome, LDL Particle Size, and Atherosclerosis: The Atherosclerosis and Insulin Resistance (AIR) Study
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