Insulin Resistance Syndrome and Fibrinolytic Activity: The Northern Sweden MONICA Study

BERNT LINDAHL,* KJELL ASPLUND,** MATS ELIASSON* AND PER-ERIC EVRIN†


Background. Many studies have, in small and highly selected study populations, described how cardiovascular risk factors tend to cluster in subjects with insulin resistance. Recently, interest has focused on possible relationships between this insulin resistance syndrome and fibrinolysis, and the role of triglycerides in this association. The present study addresses these issues in a general population.

Methods. A subsample of participants in the population-based Northern Sweden MONICA (MONItoring of trends and determinants in CArdiovascular diseases) Study, consisting of 353 men and 403 women in the 25-64 year age range, was investigated. Insulin resistance was estimated indirectly from the fasting levels of insulin and glucose. Fibrinolytic activity was measured both as plasminogen activator inhibitor type 1 (PAI-1) activity and tissue plasminogen activator (tPA) activity.

Results. Insulin resistance was highly correlated with those cardiovascular risk factors that have been associated with the insulin resistance syndrome, and to the measures of fibrinolytic activity. Subjects in the upper tertile of insulin resistance had a PAI-1 activity that was three times higher than that of the lower third in men and twice as high in women. There was a strong interaction between insulin resistance and serum triglycerides. Low versus high levels of both variables together were associated with a fivefold difference in PAI-1 activity in men and a threefold difference in women. The tPA activity was inversely correlated to both insulin resistance and serum triglycerides.

Conclusions. In a general population, the 'insulin resistance syndrome' is closely associated with low fibrinolytic activity. Serum triglycerides levels interact with insulin resistance to predict fibrinolytic activity.

Keywords: epidemiology, fibrinogen, fibrinolysis, hyperinsulism, insulin resistance, PAI-1 activity, tPA-activity, triglycerides.

During the last decade there has been increasing interest in the role of the haemostatic and fibrinolytic system in the aetiology of coronary artery disease. The majority of myocardial infarctions are due to the formation of an arterial thrombus, and the role of fibrin deposit in this process is quite obvious. However, arterial fibrin deposit could also play a role in the initiation of atherosclerosis. A high fibrinogen level is likely to increase the deposit of fibrin, whereas low fibrinolytic activity decreases the removal of this fibrin deposit. The effectiveness of fibrinolysis mainly depends on the activity of tissue plasminogen activator (tPA), which converts plasminogen to active plasmin on the surface of the thrombus, causing thrombolysis. The tPA is released from the vessel wall upon injury and is rapidly inhibited by circulating plasma plasminogen activator inhibitor type 1 (PAI-1), which is considered as the main regulator of fibrinolytic activity.

In a recent meta-analysis, fibrinogen was considered as a major cardiovascular risk factor. Age and smoking have been shown to be two of the strongest determinants of fibrinogen levels.

Several studies have demonstrated high PAI-1 levels in patients with coronary artery disease. Hamsten et al. found low tPA activity and high PAI-1 activity in young hypertriglyceridaemic men surviving a myocardial infarction.

Insulin resistance and its association with cardiovascular risk factors have been described in several reviews. Overweight and especially upper body obesity is associated with hypertension and dyslipidaemia (high serum triglycerides and low high density lipoprotein [HDL]-cholesterol). This clustering of cardiovascular risk factors has recently been referred to as the insulin resistance syndrome (IRS). The basic disturbance is thought to be peripheral insulin resistance, which
leads to compensatory hyperinsulinaemia. Insulin resistance syndrome has been estimated to be present in approximately one-sixth of a Swedish population. High levels of fasting and postchallenge insulin have been related to coronary heart disease and to asymptomatic atherosclerosis. Hyperinsulinaemia has recently been shown to predict low tPA activity in a healthy population, and high PAI-1 activity has been linked to hyperinsulinaemia and insulin resistance in several earlier studies, and to different expressions of the IRS such as obesity, hypertension, hypertriglyceridaemia and non-insulin dependent diabetes mellitus. Most of these earlier studies have been done in small and highly selected study populations and have not directly measured tPA activity.

The aim of the present study of a general population in the north of Sweden was, first, to explore the relationship between IRS and fibrinolytic activity, measured by both tPA activity and PAI-1 activity, second, to evaluate the impact of the triglyceride level on this relationship, and third, to investigate the relationship of plasma fibrinogen to IRS.

MATERIALS AND METHODS

Study Population
The present investigation was a substudy within the framework of the Northern Sweden MONICA (Monitoring of trends and determinants in Cardiovascular diseases) Study of 1990. The study population was selected by stratified randomization for sex and age (25–34, 35–44, 45–54 and 55–64 years). In each stratum, 250 individuals were invited. Of the 2000 eligible subjects, 1583 individuals participated (overall response rate 79.2%). Approximately half of the participants had a minimum fasting period of 12 hours (in practice those who came to their appointment before 11 00 am). This group was offered a 75 g oral glucose tolerance test (OGTT) according to the standards described by WHO. Subjects with known diabetes were not included. After the exclusion of individuals with missing values in any of our study parameters, 756 participants remained (353 men and 403 women). The data for these individuals formed the basis of the present study.

Methods
Together with the letter of invitation the subjects received a questionnaire on lifestyle factors and other issues related to cardiovascular disease. At the appointment with the examination team, blood pressure was measured after resting for 5 minutes, using the random zero method with the subjects in the sitting position. Bodyweight was measured using a calibrated balance. During weighing and measurement of height, the subjects removed their shoes but wore a shirt and trousers. Body mass index was calculated as weight (kg) divided by height (m) squared. The circumference of the smallest part of the waist and the thickest part of the hip in the sitting position was measured and the waist–hip ratio (WHR) was calculated.

Blood sampling. Immediately before the OGTT and exactly 2 hours after, venous samples for determination of plasma glucose and serum insulin were obtained. Glucose and insulin samples were frozen within 3 hours at −20°C.

Sampling for measurement of plasma fibrinogen, tPA and PAI-1 activity was done in the sitting position with no special rest and with minimal occlusion. Blood was drawn into 5 ml vacuum tubes (Stabilyte, Biopool AB, Umeå, Sweden) pre-filled with 0.5 ml of 0.45 mol/l citrate buffer pH 4.3. This ensured stability of tPA activity without causing appreciable haemolysis. Tubes were centrifuged at 2000 × g for 20 minutes, snapfrozen within an hour and stored in liquid nitrogen.

Laboratory procedures. Triglycerides, total cholesterol and HDL-cholesterol were measured by enzymatic methods, using commercial kits (Boehringer Mannheim GmbH, Germany). The HDL-cholesterol analyses were performed after other lipoproteins had been precipitated by phosphotungstate-magnesium.

Serum insulin was determined by radioimmunoassay (Phadeseph Insulin RIA, Pharmacia Diagnostics AB, Uppsala, Sweden). This assay has a cross reactivity with C-peptide of <0.1% and with proinsulin of 40% according to the manufacturer. Cross reactivity with proinsulin split products is not known. Plasma glucose was analysed by the hexokinase method (Boehringer Mannheim Automated Analysis for BM/Hitachi System 717).

The tPA and PAI-1 activity was determined by the coupled plasminogen/plasmin chromogenic substrate assay, Spectrolyse/fibrin kit and Spectrolyse/pl kit, respectively (Biopool). Plasma fibrinogen determinations were performed by a functional, kinetic method (Fibrinogen Kinetic, Boehringer Mannheim) using a Hitachi 717 analyser. The assay was standardized with Standard Scandinorm (Diagnostica Stago, France). Details regarding assay precision and analytical sensitivity have been published elsewhere.

Estimation of insulin resistance (IR). Laborious methods for estimating insulin resistance such as the
hyperinsulinaemic euglycaemic clamp and the insulin suppression test, are not readily used in an epidemiological setting. In the present study we have compared three simpler indices of insulin resistance; the fasting insulin level, insulin resistance (IR) according to the homeostasis model assessment (HOMA), and the value of insulin sensitivity index (ISI) according to Cederholm. All of these indices are based on the negative feedback loop between insulin and glucose.

Insulin resistance (HOMA) was calculated from the fasting insulin and glucose concentrations according to the following formula:

\[ \text{IR} = \frac{\text{insulin}}{22.5 e^{\ln \text{glucose}}} \]

This formula could be rewritten as a product of glucose and insulin, divided by a constant of 22.5. The Oxford group emphasizes that this measure of insulin resistance should be considered to be 'semi-quantitative'. A subject under 35 years of age with normal weight and normal glucose tolerance would have an insulin resistance of approximately one. The HOMA method has been found to be closely correlated with the hyperinsulinaemic euglycaemic clamp and the insulin tolerance test.

Insulin sensitivity index (ISI) was calculated according to a formula initially used by Cederholm and later by Lindahl. For further details regarding the calculation of ISI see Lindahl et al.

**Statistical analysis.** The Statistical Analysis System (SAS) was used. Distributions were expressed as means with 95% confidence intervals (CI) or as means and standard deviations of the mean (SD).

**RESULTS**

The basic characteristics of the participants in the population survey are shown in Table 1. There were no significant differences between men and women with respect to age and body mass index. Waist-hip ratio, blood pressure, triglycerides and fasting glucose were higher in men, whilst HDL-cholesterol, 2-h glucose and 2-h insulin were higher in women, who also had a significantly higher proportion of impaired and diabetic glucose tolerance.

The PAI-1 activity was higher (P < 0.05) and tPA activity lower (P < 0.05) in men compared to women (Table 2). Women had significantly higher (P < 0.001) fibrinogen levels. There were no differences in fasting insulin or in insulin resistance index according to HOMA between men and women. Men had a significantly higher (P < 0.001) ISI, when calculated according to Cederholm.

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**Table 1** Basic characteristics of the study group. The values are shown as means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 353)</th>
<th>Women (n = 403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>45.5 (11.5)</td>
<td>44.7 (11.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.7 (3.2)</td>
<td>25.2 (4.6)</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.93 (0.06)**</td>
<td>0.81 (0.06)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>129 (16.8)**</td>
<td>125 (19.6)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>83 (10.8)**</td>
<td>78 (10.5)</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/l</td>
<td>6.2 (1.2)</td>
<td>6.1 (1.3)</td>
</tr>
<tr>
<td>Serum HDL-cholesterol, mmol/l</td>
<td>1.3 (0.3)**</td>
<td>1.6 (0.4)</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/l</td>
<td>1.6 (0.8)**</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/l</td>
<td>5.4 (0.7)**</td>
<td>5.2 (0.7)</td>
</tr>
<tr>
<td>2-h plasma glucose, mmol/l</td>
<td>5.3 (1.7)**</td>
<td>5.6 (1.9)</td>
</tr>
<tr>
<td>2-h serum insulin, mU/l</td>
<td>31.9 (28.7)**</td>
<td>44.5 (56.4)</td>
</tr>
<tr>
<td>Impaired and diabetic glucose intolerance (%)</td>
<td>5.7*</td>
<td>9.7</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P < 0.01, and *** P < 0.001 for the difference between men and women.

* Fasting plasma glucose > 6.7 or 2-h glucose > 7.7 mmol/l.

* Significance testing for difference in proportions by χ² test.
TABLE 2  Main study variables. The values are shown as geometric means and 95% confidence intervals (CI)

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 353)</th>
<th>Women (n = 403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAI-1 activity, U/ml</td>
<td>7.0 (6.4-7.6)</td>
<td>6.2 (5.7-6.7)</td>
</tr>
<tr>
<td>tPA activity, IU/ral</td>
<td>0.71 (0.66-0.75)</td>
<td>0.79 (0.75-0.83)</td>
</tr>
<tr>
<td>Plasma fibrinogen, g/l</td>
<td>3.29 (3.22-3.35)</td>
<td>3.56 (3.49-3.63)</td>
</tr>
<tr>
<td>Fasting serum insulin, mll/l</td>
<td>6.2 (5-6.6)</td>
<td>5.9 (5-6.2)</td>
</tr>
<tr>
<td>Insulin resistance (HOMA)</td>
<td>1.5 (1.4-1.6)</td>
<td>1.4 (1.3-1.4)</td>
</tr>
<tr>
<td>Insulin sensitivity index (ISI)</td>
<td>105 (100-110)</td>
<td>93 (89-97)</td>
</tr>
</tbody>
</table>

TABLE 3  Pearson correlation coefficients between three different indices of insulin resistance and cardiovascular risk factors commonly associated with the insulin resistance syndrome

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 353)</th>
<th>Women (n = 403)</th>
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</thead>
<tbody>
<tr>
<td>fS-insulin</td>
<td>0.53</td>
<td>0.57</td>
</tr>
<tr>
<td>IR(HOMA)</td>
<td>0.53</td>
<td>0.58</td>
</tr>
<tr>
<td>ISI</td>
<td>-0.38</td>
<td>-0.47</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.42</td>
<td>0.49</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.43</td>
<td>0.50</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.29</td>
<td>0.38</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.33</td>
<td>0.20</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.26</td>
<td>0.15</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.14</td>
<td>0.27</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.54</td>
<td>0.49</td>
</tr>
<tr>
<td>PAI-1 activity</td>
<td>-0.42</td>
<td>-0.32</td>
</tr>
<tr>
<td>tPA activity</td>
<td>-0.41</td>
<td>-0.32</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.15</td>
<td>0.35</td>
</tr>
</tbody>
</table>

In both genders, there was a high correlation of 0.98 between IR(HOMA) and fasting insulin, whereas the correlation coefficient between IR(HOMA) and the ISI in men was -0.53 and in women -0.68.

Table 3 shows the association between insulin resistance, measured indirectly by three different indices, and 10 cardiovascular risk factors generally considered to be components of the IRS. All of the associations described in the Table were statistically significant. Fasting insulin and IR(HOMA) have a closer association than ISI to body mass index, waist-hip ratio, triglycerides and fibrinolytic variables (PAI-1 and tPA). The association between blood pressure and insulin resistance was somewhat weaker and did not differ with the different methods of calculation. The relationship between fibrinogen and insulin resistance was clearly closer in women.

This is further indicated by Table 4, showing that the fibrinogen level in women, after adjusting for age and smoking, increased significantly by increasing insulin resistance. The mean in the group with the highest tertile of IR, had a fibrinogen level that was 16% higher than the group with the lowest tertile of IR. (P < 0.001) compared to the group with the lowest tertile of IR.

Table 5 shows age-adjusted PAI-1 and tPA activity at different levels of insulin resistance. Insulin resistance (HOMA) was divided into tertiles. In men, the group with the highest insulin resistance (upper tertile) had a
**Table 5** Age-adjusted plasminogen activator inhibitor (PAI-1) and tissue plasminogen activator (tPA) activity at different levels of insulin resistance. Insulin resistance (IR) has been calculated according to the HOMA method and divided into tertiles. Mean values are shown, including 95% confidence intervals.

<table>
<thead>
<tr>
<th>Men (n = 353)</th>
<th>Women (n = 403)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IR (HOMA)</strong></td>
<td><strong>IR (HOMA)</strong></td>
</tr>
<tr>
<td>lower tertile</td>
<td>4.2 (3.6–4.8)</td>
</tr>
<tr>
<td>middle tertile</td>
<td>6.4 (5.6–7.4)**</td>
</tr>
<tr>
<td>upper tertile</td>
<td>12.7 (11.0–14.6)***</td>
</tr>
<tr>
<td>PAI-1 (U/ml)</td>
<td>0.94 (0.85–1.04)</td>
</tr>
<tr>
<td>tPA (IU/ml)</td>
<td>0.77 (0.70–0.85)**</td>
</tr>
<tr>
<td></td>
<td>0.49 (0.45–0.55)***</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01, and *p < 0.001 versus lower tertile.

PAI-1 activity of approximately three times that of the lower tertile (12.7 versus 4.2 U/ml). In women, PAI-1 activity was approximately twice as high in the upper IR tertile than in the lower tertile (9.4 versus 4.5 U/ml). These differences were highly significant (*P < 0.001). Conversely, the tPA activity in the upper tertile of IR in men was approximately half of that in the lower tertile. This difference was less pronounced in women, but was still highly significant. In women, the upper IR tertile had a tPA activity of about 75% of that in the lower tertile.

The relationships between insulin resistance, triglycerides and PAI-1 activity are illustrated by Figure 1, showing a fivefold increase in PAI-1 activity in men, when comparing the upper tertiles of IR(HOMA) and serum triglycerides with the lower tertiles. In women, the corresponding comparison showed a threefold increase in PAI-1 activity.

Figure 2 shows the associations between tPA activity, insulin resistance and serum triglycerides. The upper third of both insulin resistance and serum triglycerides had a tPA activity in men of 40% of that in the lower thirds, and in women of approximately 60%.

Multiple regression analyses were performed, using the forward stepwise strategy and a relatively restricted starting model with PAI-1 or tPA activity as the dependent variables, and age, body mass index, diastolic blood pressure, triglycerides together with IR(HOMA) as the independent variables. To avoid collinearity problems, the independent variables that were non-significant or had a low degree of association to the dependent variable, were successively rejected.
until all tolerance values exceeded 0.65. In men with PAI-1 activity as the dependent variable, the coefficient of determination ($R^2$) was 0.42, and four independent variables were included in the final model. In order of strength they were IR(HOMA), triglycerides, diastolic blood pressure and age. All of them, except age ($P < 0.01$), were highly significant ($P < 0.001$). In women $R^2$ was 0.30, and two variables remained in the model. The strongest of them was IR(HOMA), followed by body mass index ($P < 0.001$). When tPA activity was used as the dependent variable, $R^2$ decreased to 0.23 in men and 0.18 in women. In men three independent variables remained in the final model; the strongest of them was IR(HOMA), followed by body mass index and age ($P < 0.001$). Even in women three variables were left in the final model, and the strongest was body mass index, followed by triglycerides and age ($P < 0.001$). Notably, in women, IR(HOMA) was rejected from the model. There was a small, but significant, interaction term between IR(HOMA) and triglycerides in women, when PAI-1 was the dependent variable, and in men, when tPA was the dependent variable.

DISCUSSION
We have earlier shown that there is clustering of cardiovascular risk factors in a subpopulation with low insulin sensitivity and high fasting insulin levels. In the present study on a randomly selected sample of a general population, we establish that this IRS is also associated with a low fibrinolytic activity, measured as low tPA activity as a consequence of high PAI-1 activity. With the possible exception of tPA activity in women, this applies to both sexes and was shown in univariate as well as multivariate analyses.

Furthermore, the present results are in line with findings from the ARIC study showing that women have significantly higher fibrinogen levels than men. We also found that this higher fibrinogen, after adjustment for age and smoking, was significantly associated with insulin resistance/hyperinsulinaemia. This association was reduced but did not disappear, when adjustment for body mass index was included in the model or when subjects with impaired and diabetic glucose tolerance, according to WHO criteria, were excluded from the model. There was no corresponding association in males.

Precise measurements of insulin resistance are not feasible in epidemiological studies, because the methods are so laborious. In the present study we have compared three indices of insulin resistance and found that all of them showed the same association between insulin resistance and low fibrinolytic activity; this is in line with many other studies. A recent study, where insulin sensitivity was estimated by the minimal model method, showed in univariate analyses an inverse relationship between PAI-1 activity and insulin sensitivity. However, when introduced into multivariate analyses, insulin sensitivity was no longer an independent determinant of PAI-1 activity.

Our data indicate that there is a dose-response relationship between insulin resistance/hyperinsulinaemia and fibrinolysis. However, this does not necessarily imply that insulin resistance induces a suppression in the fibrinolytic activity. Intervention studies are needed to elucidate this issue. Vague et al. reduced insulin
resistance by using metformin treatment and found a simultaneous and significant reduction in PAI-1 activity.\textsuperscript{34} Other studies where insulin sensitivity increased due to fasting, increased intake of fibre, weight reduction and physical activity, have also reported concomitant reductions in PAI-1 activity.\textsuperscript{35,36}

Fasting insulin levels were closely associated with IR(HOMA) ($r = 0.98$), and both had the same power to predict the variance in PAI-1 and tPA activity, and showed approximately the same strength of associations to the other risk factors in IRS. It seems that, for practical purposes the two methods are interchangeable. However, the ISI was not as reliable as IR(HOMA) and fasting insulin at predicting the variance in PAI-1 and tPA activity and showed a lower strength of associations to the other risk factors in the IRS. We did not find any advantage in including the post-load insulin and glucose values when describing the relationships between insulin resistance/hyperinsulinaemia and fibrinolysis. This agrees with Laakso,\textsuperscript{37} who found that the fasting insulin levels, but not the post-load insulin, could be used as a relative measure of insulin resistance, especially when dealing with impaired or diabetic glucose tolerance in the population. The IR(HOMA) as a measure of insulin resistance is consistently found to be closely correlated with both the hyperinsulinaemic euglycaemic clamp and the insulin tolerance test.\textsuperscript{30,38}

Our data confirm the data of some\textsuperscript{39,40} but not all\textsuperscript{41} earlier studies, showing that there is a strong relationship between the degree of insulin resistance and the serum triglyceride levels. The nature of this relationship has yet to be established. One recent study reported that treating hypertriglyceridaemic patients with the lipid-lowering fibrate gemfibrozil concomitantly decreased both the triglyceride level and the insulin resistance.\textsuperscript{42}

The present data show that insulin resistance and hypertriglyceridaemia interact in their association with increased PAI-1 activity and/or decreased tPA activity, as shown by Figures 1 and 2. Several investigators have pointed out plasma insulin to be the main regulator of plasma PAI-1 activity, either directly, by increasing the production of PAI-1 in liver cells, or indirectly, by increasing the production of very low density lipoprotein (VLDL) triglycerides from the liver.\textsuperscript{43,44} High levels of VLDL-triglycerides have, at least in vitro, been shown to stimulate the secretion of endothelial PAI-1 from the vessel wall.\textsuperscript{45} However, short-term infusions of insulin do not seem to affect the PAI-1 activity.\textsuperscript{46} One possibility is that it is proinsulin and split proinsulin, and not plasma insulin per se, that stimulate the secretion of PAI-1.\textsuperscript{47} Unfortunately, in the assay used in the present study, insulin cross-reacts strongly with proinsulin.

Another recent finding that has the potential to be the common origin of IRS is the strong association between low birthweight and the different aspects of IRS (hypertension, dyslipidaemia, impaired glucose tolerance, non-insulin-dependent diabetes mellitus and ischaemic heart disease). This fetal hypothesis claims that reduced growth in utero impairs the development of the pancreas leading to a $\beta$-cell deficiency, and later in life to IRS.\textsuperscript{48}

In summary, we conclude that the earlier described clustering of cardiovascular risk factors referred to as 'the insulin resistance syndrome', should also include low fibrinolytic activity. The mechanisms by which insulin resistance/hyperinsulinaemia affect fibrinolysis are still unclear, but the serum triglyceride level seems to be involved in the process. In women, fibrinogen is also associated with IRS.

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