Insulin Resistance as a Risk Factor for Carotid Atherosclerosis
A Comparison of the Homeostasis Model Assessment and the Short Insulin Tolerance Test

Harald Sourij, MD; Isabella Schoenlzer, MD; Peter Dittrich, PhD; Bernhard Paulweber, MD; Bernhard Iglseder, MD; Thomas C. Wascher, MD

Background and Purpose—The independent contribution of insulin resistance to atherosclerosis is still under debate. We compared associations of 2 different indices of insulin resistance, the Homeostasis Model Assessment (HOMA) index and kITT from a short insulin tolerance test with carotid atherosclerosis.

Methods—A total of 1771 middle-aged white patients were investigated. Intima media thickness (IMT) and extent of carotid atherosclerosis were quantified by ultrasound. HOMA was calculated and an insulin tolerance test was performed.

Results—HOMA and kITT were significant predictors for average carotid IMT (P<0.001). After adjustment for age and the components of the metabolic syndrome, HOMA still remained an independent predictor for IMTavg (P=0.02), whereas kITT failed to do so. HOMA and kITT were also predictive (P=0.004 and P=0.024) for carotid plaques and extent of carotid atherosclerosis (P<0.001). After adjustment for age and the components of the metabolic syndrome, neither HOMA nor kITT were independently predictive any more.

Conclusions—Our results provide evidence that HOMA rather than kITT is associated with carotid atherosclerosis and that the association is largely explained by the clustered expression of the components of the metabolic syndrome. (Stroke. 2008;39:1349-1351.)

Key Words: atherosclerosis ■ intima media thickness ■ metabolic syndrome

The association among insulin resistance, compensatory hyperinsulinemia, and atherosclerosis has not been clearly established as yet. Surrogate markers for insulin resistance such as fasting insulin, the 2-hour postload insulin in the Paris Prospective Study,1 or the area under the plasma resistance curve during an oral glucose tolerance test in the Helsinki Policemen Study2 predicted morbidity and mortality from coronary artery disease.

Carotid artery intima media thickness (IMT) and the more progressive atherosclerotic state of carotid plaques are highly predictive for hard cardiovascular end points such as myocardial infarction or stroke.3 Thus, the aim of our study was to compare for the first time the associations of 2 different, more precise insulin sensitivity indices, Homeostasis Model Assessment (HOMA)4 and kITT from the short insulin tolerance test (ITT)5 with the extent of carotid atherosclerosis in a large population sample.

Materials and Methods
A total of 1771 subjects (1108 males aged 40 to 55 years and 663 females aged 50 to 65 years) participated in the Salzburg Atherosclerosis Prevention program in subjects at High Individual Risk (SAPHIR).6 Briefly, healthy middle-aged subjects without established, clinically manifest vascular disease, congestive heart failure, valvular heart disease, chronic alcohol or drug abuse, or body mass index >40 kg/m2 were included. The purpose of SAPHIR is to investigate cross-sectionally as well as prospectively predictors of vascular disease as well as to perform specific interventions in identified high-risk subjects. The study was approved by the local ethics committee and informed consent was obtained from all participants.

In all patients, an ITT was performed5 and HOMA index was calculated: (fasting plasma glucose (mmol/L))×fasting serum insulin (µU/mL)/22.5.

Metabolic syndrome (MetS) was diagnosed by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults criteria7 modified with regard to fasting plasma glucose levels (≥5.5 mmol/L).

Carotid atherosclerosis was determined by B-mode ultrasound (ATL HDI 3000-CV; Phillips Medical Systems) according to the Asymptomatic Carotid Artery Plaque Study protocol.8 Average carotid IMT (IMTavg) was calculated and a B-score was formed as follows: 0=no alteration, 1=wall thickness >1 mm, 2=plaque <2 mm, 3=plaque 2 to 3 mm, 4=plaque >3 mm, and 5=total
Table 1. Characteristics of the SAPHIR Population

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Males</th>
<th>Females</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1705</td>
<td>1062</td>
<td>643</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>51.7±6.1</td>
<td>49.0±5.5</td>
<td>56.1±4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index kg/m²</td>
<td>26.7±4.0</td>
<td>26.8±3.7</td>
<td>26.5±4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>94.2±12.5</td>
<td>97.6±10.4</td>
<td>88.6±13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.89±0.08</td>
<td>0.92±0.07</td>
<td>0.84±0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134±13</td>
<td>135±13</td>
<td>131±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82±8</td>
<td>83±8</td>
<td>81±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.9±1.0</td>
<td>5.8±1.0</td>
<td>6.1±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mmol/L</td>
<td>3.7±0.9</td>
<td>3.8±0.9</td>
<td>3.7±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
<td>1.6±0.4</td>
<td>1.4±0.3</td>
<td>1.8±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.4±1.0</td>
<td>1.5±1.1</td>
<td>1.2±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.1±0.5</td>
<td>5.1±0.5</td>
<td>5.0±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin, μU/mL</td>
<td>7.2±4.8</td>
<td>7.4±5.3</td>
<td>7.0±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.7±1.2</td>
<td>1.7±1.3</td>
<td>1.6±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>kITT</td>
<td>4.2±1.3</td>
<td>4.2±1.4</td>
<td>4.3±1.2</td>
<td>0.042</td>
</tr>
<tr>
<td>Average IMT, mm</td>
<td>0.795±0.119</td>
<td>0.791±0.119</td>
<td>0.795±0.119</td>
<td>NS</td>
</tr>
<tr>
<td>Single B-score &gt;2, n (%)</td>
<td>136 (7.9)</td>
<td>86 (8.1)</td>
<td>50 (7.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Sum B-score &gt;3, n (%)</td>
<td>294 (17.2)</td>
<td>172 (16.2)</td>
<td>122 (18.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>292 (17.1)</td>
<td>186 (17.5)</td>
<td>106 (16.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Unless indicated, data are given as mean±SD. P is given for analysis of variance. *P for chi-squared test males versus females. NS indicates not significant.

closure of the lumen. A single B-score >2 on any measure–point was defined as advanced carotid plaque. A sum B-score >3, containing values of the common carotid artery and internal carotid artery from both sides was taken as advanced carotid atherosclerosis.

Sixty-six patients with manifest diabetes (history and/or treatment) were excluded from the present analysis.

Statistical analyses were performed with SPSS 14.0 statistical package (SPSS Inc). Analysis of variance or chi-squared tests were performed to compare groups. Multivariate regression analysis with IMT as the dependent variable was performed with HOMA and kITT, respectively. Logistic regression analysis was performed for single B-score >2 and sum B-score >3. The level of significance was set at P<0.05.

Results

Clinical and biochemical characteristics of the study participants are presented in Table 1. To be more comparable with regard to cardiovascular risk, females were 10 years older than males on inclusion criteria. Thus, carotid IMT was almost identical in male and female subjects (0.791±0.12 versus 0.795±0.12 mm, P=not significant).

Multivariate regression models with HOMA and kITT were performed. Both were highly significant predictors for IMTavg (P<0.001), even after adjustment for age (P<0.001; Table 2). After further adjustment for the components of the MetS, HOMA remained a significant predictor for IMTavg (P=0.001), whereas kITT was not predictive any more. Age, waist circumference, high-density lipoprotein cholesterol, and systolic and diastolic blood pressure were significant, independent predictors in both models (data not shown). Finally, we calculated models, including either HOMA or kITT, and adjusted for age and the presence of a manifest MetS. Neither HOMA nor kITT remained independently predictive parameters for IMTavg in that model.

To analyze the association with carotid plaques, logistic regression analysis was performed and both HOMA and kITT were predictive (P=0.004 and P=0.024) for carotid plaques in the unadjusted model. After adjustment for age, HOMA remained predictive (P=0.016), whereas kITT failed to do so. After further adjustment for all components of the MetS,
neither HOMA nor kITT were independently predictive any more.

Regarding advanced carotid atherosclerosis, both insulin sensitivity indices remained significant predictors after adjustment for age in the logistic regression analysis ($P<0.001$) but lost significance after adjustment for the components of the MetS.

Analyses were also performed in males and females separately and results were not different from those observed in the entire cohort (data not shown).

**Discussion**

Our study, to the best of our knowledge, for the first time compares cross-sectionally 2 different measurements for whole body insulin resistance.

Even if HOMA and kITT are strongly correlated in our study, best characterized by a quadratic function ($r^2=0.306$, $P<0.001$), they seem to describe different phenotypes of insulin resistance (data not shown). An explanation might be that the contribution of the different components of whole body insulin resistance, hepatic and peripheral insulin resistance, varies between these 2 indices. Because HOMA is calculated from basal plasma insulin and basal plasma glucose, it expresses predominantly the ability of basal insulin to suppress hepatic glucose production in a fasting state. ITT, in contrast, is more influenced by peripheral glucose disposal after an insulin application reflecting peripheral insulin resistance.

In our observation, insulin resistance estimated by HOMA and kITT was a strong predictor of carotid IMT in univariate analyses. After adjustment for age and the components of the MetS, only HOMA remained predictive for IMT$_{avg}$. Most of the studies investigating the impact of insulin resistance on carotid atherosclerosis or atherosclerotic vascular events did not or partially adjusted their results for the phenotypic expressions of the MetS, despite the fact they all are established vascular risk factors.

The fact that HOMA was significantly associated with IMT$_{avg}$ after full adjustment for age and the components of the MetS may provide a hint to the importance of hepatic insulin resistance for atherogenesis.

Interestingly, this association disappeared when we adjusted for age and the presence of the MetS instead of the single components. This observation, in our opinion, indicates the importance of the cluster concept of the MetS.

In conclusion, our results provide evidence that HOMA rather than kITT is associated with carotid atherosclerosis and that most of that association is dependent on the clustered expression of components of the MetS observed in insulin resistant subjects.

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**Disclosures**

None.

**References**


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