Circulating Insulin-Like Growth Factor-1 and Insulin-Like Growth Factor Binding Protein-3 Are Associated With Early Carotid Atherosclerosis

Shin-ichi Kawachi, Noriyuki Takeda, Akihiko Sasaki, Yoshiaki Kokubo, Kazuhisa Takami, Hiroshi Sarui, Makoto Hayashi, Noriyoshi Yamakita, Keigo Yasuda

Objective—Growth hormone (GH)–insulin-like growth factor (IGF)-1 axis regulates growth and survival of vascular cells and cardiomyocytes. The role of GH–IGF-1 axis in cardiovascular disease is controversial.

Methods and Results—We assessed the association of circulating levels of IGF-1 and IGF binding protein-3 (IGFBP-3) with early carotid atherosclerosis and atherosclerotic risk factors in 330 Japanese men (age 51.6 ± 8.6 years, range 29 to 77, body mass index [BMI] 23.6 ± 2.9 kg/m²). Intima-media thickness (IMT) of the common carotid artery was measured by ultrasound. Abdominal visceral adipose and subcutaneous adipose tissue area by computer-assisted tomographic scan were determined. Correlation coefficients were calculated by partial correlation analysis. BMI and plasma insulin showed positive associations with circulating IGF-1 and IGFBP-3. Subcutaneous adipose tissue was correlated with IGF-1. High-density lipoprotein cholesterol was inversely associated with IGF-1. Blood pressure, total cholesterol, triglyceride, and visceral adipose tissue were positively associated with IGFBP-3. IGF-1 and IGFBP-3 were associated with carotid IMT independent of age, BMI, blood pressure, and insulin. Insulin was associated with carotid IMT in univariate analysis. However, it was not correlated with carotid IMT in the multivariate analyses which included IGF-1 or IGFBP-3 as a covariate.

Conclusion—Increased circulating IGF-1 and IGFBP-3 may be stimulators of atherosclerosis. (Arterioscler Thromb Vasc Biol. 2005;25:617-621.)

Key Words: insulin-like growth factor-1 ■ insulin-like growth factor binding protein-3 ■ atherosclerosis ■ cardiovascular disease ■ metabolic syndrome
and IGFBP-3 have opposite predictive roles in the risk of several types of cancer. It would be interesting to see whether this is the case also for atherosclerosis.

Methods

Study Subjects

The subjects were 330 Japanese men aged 29 to 77 years (mean±SD, 51.6±8.6 years) who participated in a health check-up program conducted in Matsunami General Hospital, an urban hospital located in Gifu Prefecture, Japan, in the year 2000. Those who had a previous history of acute myocardial infarction, angina, or stroke and those who had ischemic changes on the ECG taken in this study were excluded from the study. All subjects gave informed consent before entry. The study was approved by the ethics committee of Matsunami General Hospital and of Gifu University School of Medicine.

Data Collection and Measurements

The subjects came to the hospital in the morning and stayed there for 36 hours until they had completed all scheduled medical examinations. The health check program that they attended, as previously reported,17,18 included blood chemistry, a standard oral 75g glucose tolerance test, ECG, chest X-ray, barium examination of the upper gastrointestinal tract, and computer-assisted tomographic scan of the abdomen. Plasma glucose and insulin were measured by a glucose oxidase method and a double antibody radioimmunoassay, respectively. Area under the curve of plasma glucose during 75g oral glucose tolerance test (AUC-PG) was calculated as a measure of glucose tolerance. A parameter of insulin resistance was calculated from a homeostasis model (HOMA-R). Serum total cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol were measured by methods described elsewhere.17 Serum IGF-1 was measured by an immunoradiometric assay using a commercially available kit (Yuka Medias). The limit of detection was 0.3 ng/mL. Intra- and interassay coefficients of variation (CVs) were 5.2% and 7.7%, respectively. Serum IGFBP-3 was measured by an immunoradiometric assay kit (Diagnostic Systems Laboratories Inc; detection limit 1 ng/mL, intra-assay CV 2.6%, interassay CV 6.9%).

Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m). Abdominal visceral (VAT) and subcutaneous adipose (SAT) tissue areas were measured by computer-assisted tomographic scan as described elsewhere.17 IMT of the common carotid artery was measured by B-mode ultrasound according to the method of Pignoli et al20 modified by us.17 A longitudinal 2D ultrasound image of the common carotid artery was scanned with a 10-MHz linear array transducer while patients were in a supine position. The greatest IMT and those measured 1 cm upstream and downstream from the site of the greatest IMT were measured bilaterally. In total, 6 IMT values were obtained for each subject. The average of these measurements was calculated and used for the statistical analyses. The measurement of IMT was performed by a single physician throughout the study, so as to avoid interobserver variation. Smoking status was obtained by a self-administered questionnaire. Smoking status was expressed by the Brinkman index, which is calculated as the number of cigarettes per day multiplied by years of smoking.

Statistical Analysis

The results were expressed as mean±SD. To improve normality of the distribution, triglyceride, insulin, and HOMA-R were transformed to their logarithms before statistical analysis. The median and range were also given for these variables. Statistical analyses were made using the Statistical Analysis System version 6.12 for Windows (SAS Institute Inc). Relations between variables were evaluated by partial correlation analysis. Because we tried to improve skewness in the distribution of the Brinkman index but we could not approximate normality by logarithmic, square root, and other trans-

Results

Clinical and Laboratory Characteristics

Table 1 shows the clinical and laboratory characteristics of the study subjects. They were relatively lean compared with black and white American men of a similar age range. Their mean BMI, however, accords well with the figure obtained from a survey of a large sample conducted in Japan.21 According to recent diagnostic criteria,22–24 there are 20 subjects with type 2 diabetes mellitus, 72 with hypertension, and 96 with serum lipid abnormalities, including those who had high or very high total cholesterol or triglyceride or low HDL-cholesterol.

Associations of the IGF-1 Axis With Adiposity and Metabolic Variables

As shown in Table 2, after adjustment for age, BMI was correlated with circulating IGF-1 and IGFBP-3. SAT was correlated with IGF-1. VAT was correlated with IGFBP-3. Blood pressure was not correlated with IGF-1. However, there was a positive correlation between blood pressure and IGFBP-3. Total cholesterol and log triglyceride were correlated positively with IGFBP-3. HDL-cholesterol was inversely correlated with IGF-1. Both log fasting plasma insulin and log HOMA-R were correlated positively with IGF-1 and IGFBP-3. Fasting plasma glucose and AUC-PG were not associated with IGF-1 or IGFBP-3. Brinkman index was not

### Table 1. Clinical and Laboratory Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>SD (Median, Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>51.6</td>
<td>8.6</td>
</tr>
<tr>
<td>Brinkman index</td>
<td>553.1</td>
<td>561.2 (455, 0–2960)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>123.6</td>
<td>15.1</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.9</td>
<td>10.5</td>
</tr>
<tr>
<td>VAT, cm²</td>
<td>110.0</td>
<td>49.1</td>
</tr>
<tr>
<td>SAT, cm²</td>
<td>129.6</td>
<td>56.7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>197.1</td>
<td>31.4</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>140.0</td>
<td>93.3 (116.0, 30–803)</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>55.9</td>
<td>15.9</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dl</td>
<td>101.1</td>
<td>13.0</td>
</tr>
<tr>
<td>Fasting plasma insulin, µU/ml</td>
<td>6.4</td>
<td>3.7 (5.5, 2.2–32.0)</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>1.63</td>
<td>1.02 (1.39, 0.50–8.05)</td>
</tr>
<tr>
<td>AUC-PG, mg/dl min</td>
<td>16237</td>
<td>4323</td>
</tr>
<tr>
<td>IGF-1, ng/ml</td>
<td>160.7</td>
<td>36.9</td>
</tr>
<tr>
<td>IGFBP-3, ng/ml</td>
<td>3193.2</td>
<td>496.6</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.66</td>
<td>0.12</td>
</tr>
</tbody>
</table>

VAT indicates visceral abdominal adipose tissue; SAT, subcutaneous abdominal adipose tissue; HOMA-R, homeostasis model assessment of insulin resistance; AUC-PG, area under the curve of plasma glucose during 75g oral glucose tolerance test; IMT, common carotid arterial intima-media thickness.
TABLE 2. Correlation Between the IGF-1 Axis and Body Adiposity, Blood Pressure, and Metabolic Variables (Partial Correlation Coefficient After Adjustment for Age)

<table>
<thead>
<tr>
<th>Variables</th>
<th>IGF-1</th>
<th></th>
<th>IGFBP-3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.206</td>
<td>0.0002</td>
<td>0.154</td>
<td>0.0052</td>
</tr>
<tr>
<td>VAT</td>
<td>0.098</td>
<td>0.0748</td>
<td>0.197</td>
<td>0.0003</td>
</tr>
<tr>
<td>SAT</td>
<td>0.147</td>
<td>0.0075</td>
<td>0.083</td>
<td>0.1345</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.105</td>
<td>0.0560</td>
<td>0.161</td>
<td>0.0034</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.084</td>
<td>0.1295</td>
<td>0.128</td>
<td>0.0201</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.002</td>
<td>0.9728</td>
<td>0.211</td>
<td>0.0001</td>
</tr>
<tr>
<td>log triglyceride</td>
<td>0.082</td>
<td>0.1361</td>
<td>0.208</td>
<td>0.0002</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>−0.154</td>
<td>0.0052</td>
<td>−0.037</td>
<td>0.5013</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>0.084</td>
<td>0.1301</td>
<td>0.101</td>
<td>0.0674</td>
</tr>
<tr>
<td>Log fasting plasma insulin</td>
<td>0.226</td>
<td>0.0001</td>
<td>0.113</td>
<td>0.0401</td>
</tr>
<tr>
<td>Log HOMA-R</td>
<td>0.228</td>
<td>0.0001</td>
<td>0.126</td>
<td>0.0222</td>
</tr>
<tr>
<td>AUC-PG</td>
<td>−0.040</td>
<td>0.4661</td>
<td>0.053</td>
<td>0.3381</td>
</tr>
<tr>
<td>Brinkman index*</td>
<td>−0.005</td>
<td>0.9263</td>
<td>0.047</td>
<td>0.3911</td>
</tr>
</tbody>
</table>

VAT indicates visceral abdominal adipose tissue; SAT, subcutaneous abdominal adipose tissue; HOMA-R, homeostasis model assessment of insulin resistance; AUC-PG, area under the curve of plasma glucose during 75g oral glucose tolerance test.

*Spearman rank correlation test was used to calculate correlation coefficient.

The IGF-1 Axis and Carotid IMT

Both circulating IGF-1 and IGFBP-3 were associated with carotid IMT after adjustment for age (Table 3). Among the other variables tested, BMI, blood pressure, log fasting plasma insulin, and log HOMA-R showed significant correlations with carotid IMT. Correlation between IMT and Brinkman index was analyzed by Spearman rank correlation test after adjustment for age. Brinkman index was not significantly correlated with IMT.

To evaluate the confounding effects of these variables on the association between the IGF-1 axis and carotid IMT, 2 multivariate models were tested (Table 4). Both models contain all variables that showed a significant association with IMT in partial correlation analyses after adjustment for age. Then age, BMI, systolic blood pressure, and log fasting plasma insulin were included as independent variables. In addition, IGF-1 and IGFBP-3 were included in model 1 and 2, respectively. Because there were close correlations between systolic and diastolic blood pressure (r=0.685, P=0.0001), log fasting plasma insulin, and log HOMA-R (r=0.976, P=0.0001), we excluded diastolic blood pressure and log HOMA-R from our multivariate models. Both IGF-1 and IGFBP-3 were positively correlated with carotid IMT in the multivariate analyses. It should be noted that neither log fasting plasma insulin nor BMI was an independent correlate in these multivariate models.

TABLE 3. Correlation Between Carotid IMT and Body Adiposity, Blood Pressure, Metabolic Variables, and the IGF-1 Axis (Partial Correlation Coefficient After Adjustment for Age)

<table>
<thead>
<tr>
<th>Variables</th>
<th>IMT</th>
<th></th>
<th>IMT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.156</td>
<td>0.0047</td>
<td>−0.006</td>
<td>0.9130</td>
</tr>
<tr>
<td>VAT</td>
<td>0.095</td>
<td>0.0863</td>
<td>0.183</td>
<td>0.0009</td>
</tr>
<tr>
<td>SAT</td>
<td>0.002</td>
<td>0.9792</td>
<td>0.145</td>
<td>0.0083</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.001</td>
<td>0.9792</td>
<td>0.000</td>
<td>0.9792</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.040</td>
<td>0.4727</td>
<td>0.005</td>
<td>0.9231</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>−0.005</td>
<td>0.9263</td>
<td>0.081</td>
<td>0.1448</td>
</tr>
<tr>
<td>log triglyceride</td>
<td>0.134</td>
<td>0.0417</td>
<td>0.141</td>
<td>0.0105</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>0.101</td>
<td>0.0661</td>
<td>0.191</td>
<td>0.0010</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>0.170</td>
<td>0.0019</td>
<td>0.088</td>
<td>0.1107</td>
</tr>
<tr>
<td>Log fasting plasma insulin</td>
<td>0.040</td>
<td>0.4721</td>
<td>−0.005</td>
<td>0.9263</td>
</tr>
<tr>
<td>Log HOMA-R</td>
<td>0.040</td>
<td>0.4721</td>
<td>0.040</td>
<td>0.4721</td>
</tr>
</tbody>
</table>

VAT indicates visceral abdominal adipose tissue; SAT, subcutaneous abdominal adipose tissue; HOMA-R, homeostasis model assessment of insulin resistance; AUC-PG, area under the curve of plasma glucose during 75g oral glucose tolerance test; IMT, common carotid arterial intima-media thickness.

*Spearman rank correlation test was used to calculate correlation coefficient.

**Discussion**

We have found that serum IGF-1 and IGFBP-3 levels are associated with carotid IMT in Japanese men. The results are significant, because the prevailing view is that decreased activity of the GH–IGF-1 axis may predispose to cardiovascular disease.

The effect of IGF-1 axis on vascular cells is complex.1,2 IGF-1 stimulates vascular smooth muscle cell (VSMC) pro-

TABLE 4. Multivariate Models With Carotid IMT as the Dependent Variable

<table>
<thead>
<tr>
<th>Variables</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1</td>
<td>0.137</td>
<td>0.0130</td>
</tr>
<tr>
<td>AGE</td>
<td>0.393</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.066</td>
<td>0.2377</td>
</tr>
<tr>
<td>SBP</td>
<td>0.153</td>
<td>0.0055</td>
</tr>
<tr>
<td>Log FPI</td>
<td>0.040</td>
<td>0.4721</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1</td>
<td>0.129</td>
<td>0.0201</td>
</tr>
<tr>
<td>AGE</td>
<td>0.379</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.066</td>
<td>0.2354</td>
</tr>
<tr>
<td>SBP</td>
<td>0.145</td>
<td>0.0088</td>
</tr>
<tr>
<td>Log FPI</td>
<td>0.055</td>
<td>0.3219</td>
</tr>
</tbody>
</table>

Partial correlation coefficient between carotid IMT and each variable was calculated after adjustment for all other variables in the model. IMT indicates common carotid arterial intima-media thickness; SBP, systolic blood pressure; Log FPI, log fasting plasma insulin.
liferation and migration to promote neointimal formation. On
the other hand, IGF-1 may serve to protect against plaque
instability and rupture by suppressing VSMC apoptosis and
increasing VSMC elastogenesis.

Previous studies demonstrated decreased circulating levels
of total or free IGF-1 or IGFBP-3 in patients with coro-

nary artery disease. In contrast, we found that carotid IMT
increased with the levels of IGF-1 and IGFBP-3 in

Japanese men. However, our results are not contradictory
to the previous studies. The difference in study populations,
that is, patients with manifest heart disease versus healthy men,
seems to account largely for the discordance between ours
and the above-mentioned studies.

Systemic circulatory IGF-1 levels are regulated by com-

plex mechanisms. Nutritional status and physical activity are
important determinants of circulating IGF-1 levels. There
is evidence suggesting that IGF-1 levels can be downregulated
by cytokines. It is possible that IGF-1 levels in patients with
manifest coronary artery disease may be affected by in-
creased production of cytokines which was observed in acute
myocardial infarction, self-restiction of physical activity to
prevent anginal episodes, and poor nutrition during acute
illness. In this regard, it is notable that several investigators
have demonstrated time-dependent changes in circulating
IGF-1 levels in patients with acute myocardial infarction.
Conti reported that circulating IGF-1 levels were markedly
reduced in the acute phase of myocardial infarction but were
normalized after 1 year. Furthermore, Lee et al found that
patients with acute myocardial infarction had higher circulat-
ing levels of IGF-1 and IGFBP-3 on day 1 of admission to
hospital, with the levels decreasing through day 2 and day 3
and then bouncing back to levels higher than control levels
from day 7 to day 21.

We studied subclinical early carotid atherosclerosis by
measuring carotid IMT. The study subjects were healthy men
without active illness. Those who had a previous history of
cardiovascular disease or ischemic ECG changes were ex-
cluded. The features of the study probably allowed us to
evaluate the association between circulating IGF-1 and
IGFBP-3 and carotid atherosclerosis with minimal, if any,
effects of cardiovascular disease on levels of IGF-1 and
IGFBP-3. This study suggests that increased circulating
IGF-1 and IGFBP-3 may promote atherosclerosis.

The role of the GH–IGF-1 axis in atherosclerosis was ini-

tially implicated in patients with pituitary disorders. In-
crease in carotid IMT was reported in patients with GH
deficiency and also in those with GH excess. This study
extended these early studies to subjects without pituitary
disorders. It is interesting to note that there may be a
U-shaped curve between GH–IGF-1 axis activity and ather-
sclerosis. Although metabolic abnormalities associated with
both GH deficiency and excess and the direct effect of
GH–IGF-1 on vascular cells probably contribute to form such
a U-shaped curve, the mechanisms underlying such a relation-
ship need to be elucidated.

IGFBP-3 is a member of 6 IGFBPs, which associate with
IGF-1 and IGF-II with high affinity. IGFBP-3 is the most
abundant IGFBP in the circulation. For years, the role of
IGFBPs was thought to be confined to preventing IGFs from
binding the receptor and activating the cellular signaling
pathways. In recent years, however, accumulating evidence
indicates that IGFBPs are also able to modulate IGF actions
positively. Furthermore, they may exert IGF-independent
effects. In this study, circulating IGFBP-3 levels were
related with carotid IMT. Because there was a close
association between circulating levels of IGF-1 and IGFBP-3,
it is difficult to statistically determine whether either pos-
sesses real linkage with carotid IMT. In contrast with nega-
tive associations between IGFBP-3 and cancer risk after
adjustment for IGF-1, the association between IGFBP-3 and
carotid IMT was eliminated after adjustment for IGF-1 in our
study. The role of IGFBP-3 in atherosclerosis seems different
from its role in certain cancers.

Recently, Juul demonstrated that the low IGF-1 and high
IGFBP-3 predicted increased risk of ischemic heart disease
with a case control study which was conducted in a large
prospective study on cardiovascular epidemiology. Their
results are opposite to ours in terms of IGF-1 but similar for
the role of IGFBP-3. However, if we look at their data
closely, there were no differences in the levels of IGF-1 and
IGFBP-3 between their cases with ischemic heart disease and
controls before statistical adjustment. The difference in the
levels of IGF-1 emerged after adjustment for IGFBP-3 and
vice versa. Interpretation of these analyses is difficult because
of colinearity between IGF-1 and IGFBP-3.

Although the correlation coefficients of IGF-1 and
IGFBP-3 with carotid IMT in our study were rather weak
compared with that between age and carotid IMT, they were
comparable to that of blood pressure with carotid IMT. Aging
influence on carotid IMT was noted in a number of previous
studies and is generally attributed to exposure of arterial wall
to various risk factors. However, even in subjects without major cardiovascular risk
factors, carotid IMT increased with age. Thus it may be
possible that increasing IMT with aging may reflect a specific
effect of aging on arterial wall other than atherosclerosis.

In our study, it should be noted that circulating IGF-1
levels were correlated with insulin levels. The association
between IGF-1 and insulin may reflect the effect of insulin to
increase hepatic IGF-1 production, or circulating levels of
both hormones may be determined by common nutritional
and other causal factors. For example, nutritional surfeit
which upregulates circulating IGF-1 can lead to increased
adiposity, which in turn results in hyperinsulinemia. The
association between IGF-1 and insulin raises another impor-
tant issue. Hyperinsulinemia is an important feature of the
insulin resistance syndrome and has been noted to be a
predictor of coronary artery disease in several prospective
studies. In our multivariate models, IGF-1 and IGFBP-3
were independent correlates with carotid IMT, whereas insu-
lin was not. Because IGF-1 is a much more potent mitogenic
factor than insulin itself, there is a possibility that IGF-1
mediates at least partly the link between hyperinsulinemia
and atherosclerosis.

Because this study is cross-sectional in nature, a causal
relationship cannot be established. However, the association
between carotid IMT and circulating IGF-1 and IGFBP-3 in
an apparently healthy population has important implications for the pathogenesis of early atherosclerosis.

Acknowledgments
This work was supported by a research grant from the Japanese Ministry of Education, Science, and Culture (No. 12218214). We express our deep gratitude to the late Rieko Takami, MD, for her invaluable contribution to the study. We are thankful to the staff members of Human Dock at Matsunami General Hospital who collaborated in the execution of the study.

References
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