Leptin:Adiponectin Ratio Is an Independent Predictor of Intima Media Thickness of the Common Carotid Artery

Giuseppe Danilo Norata, PhD; Sara Raselli, PhD; Liliana Grigore, MD, PhD; Katia Garlaschelli, BSc; Elena Dozio, BSc; Paolo Magni, MD, PhD; Alberico L. Catapano, PhD

Background and Purpose—The evaluation of the leptin:adiponectin ratio (L:A) has been suggested as an atherosclerotic index in patients with type 2 diabetes and a useful parameter to assess insulin resistance in patients with and without diabetes.

Methods—We investigated, therefore, the relationship between L:A ratio and intima media thickness (IMT), an independent predictor of cardiovascular disease, in 110 healthy males.

Results—L:A ratio was significantly correlated to body mass index, waist, hip, waist-to-hip ratio, systolic blood pressure, IMT, high-density lipoprotein, apolipoprotein A-I, glucose, and the homeostasis model of insulin resistance–revised. No significant correlation was observed with age, diastolic blood pressure, low-density lipoprotein, triglycerides, apolipoprotein B, ApoB/ApoA-I ratio, insulin, alanine transaminase, γ-glutamyl-transferase, and resistin. In addition, when the relationship between IMT and adiponectin or leptin alone was analyzed, only leptin plasma levels significantly associated with IMT ($r=0.301$, $P<0.01$). In a multiple regression analysis including in the statistical model the risk factors known to affect IMT (age, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol, triglycerides, total cholesterol, body mass index, glucose, and L:A ratio), we observed that only age, L:A, and glucose were independent predictors of IMT. As expected, obese subjects (body mass index $>30$ kg/m$^2$) showed a significantly higher L:A ratio compared with nonobese subjects (1.20 versus 0.42, respectively, $P<0.001$); in addition, subjects with the metabolic syndrome showed a significantly higher L:A ratio level (0.79) compared with subjects without (0.52) ($P<0.01$).

Conclusions—We show here that the L:A ratio is a powerful independent predictor of IMT in healthy subjects and correlates with several anthropometric, metabolic, and clinical parameters better than each single adipokine. (Stroke. 2007;38:2844-2846.)

Key Words: body mass index • IMT • leptin:adiponectin ratio • waist-to-hip ratio

Several clinical studies have shown that elevated leptin plasma levels predict acute cardiovascular events, restenosis after coronary angioplasty, and cerebral stroke independently of traditional risk factors.1 Leptin and adiponectin are mainly secreted by the adipose tissue. Their circulating concentrations are increased and reduced, respectively, in obese and/or diabetic subjects. Several experimental studies have shown that increased leptin may directly or indirectly (through promoting insulin resistance?) exert multiple action at the cardiovascular level,1 whereas reduction or lack of adiponectin, like in KO mice, results in accelerated atherosclerotic progression.2

More recently, the evaluation of the leptin:adiponectin ratio (L:A) has been suggested as an atherosclerotic index in patients with type 2 diabetes and a useful parameter to assess insulin resistance in patients with and without diabetes.3–5 We investigated, therefore, the relationship among L:A ratio, intima media thickness (IMT), and other cardiometabolic parameters in healthy males.

Materials and Methods

A total of 110 healthy males randomly selected from the general population (29 to 78 years old)6 were enrolled in this study. Subjects who presented with at least one of the following criteria—use of drugs for dyslipidemia or diabetes, presence of liver or kidney disease, and thyroid dysfunction—were excluded. The study was approved by the ethics committee of the Centre for the Study of Atherosclerosis (University of Milan, Italy) and the participating subjects signed an informed consent. Measurement of biochemical parameters and clinical outcome were performed with standard procedures and are described elsewhere.6,7 Briefly glucose, insulin and lipids were measured using the Cobas Mira Plus analyser (Horiba, ABX, France). ApoA-I and ApoB were measured following turbidimetric analysis and processing in the Cobas Mira Plus.

Received February 16, 2007; final revision received March 28, 2007; accepted April 4, 2007.

From the Centro SISA per lo Studio della Aterosclerosi (G.D.N., S.R., L.G., K.G., A.L.C.), Ospedale Bassini, Cinisello Balsamo, Milan, Italy; the Department of Pharmacological Sciences (G.D.N., A.L.C.), University of Milan, Italy; and the Institute of Endocrinology (E.D., P.M.), University of Milan, Italy.

Correspondence to Giuseppe Danilo Norata, Department of Pharmacological Sciences, Via Balzaretti 9, 20100 Milano, Italy. E-mail danilo.norata@unimi.it

© 2007 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.107.485540
Table 1. Clinical and Anthropometric Parameters and Their Correlations With the L:A Ratio

<table>
<thead>
<tr>
<th>Subjects (n=110), mean (SD)</th>
<th>ρ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.18</td>
<td>0.35</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>0.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.30</td>
<td>0.014</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>0.27</td>
<td>0.02</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>0.35</td>
<td>0.10</td>
</tr>
<tr>
<td>Homeostasis model of insulin resistance–revised</td>
<td>0.46</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.22</td>
<td>0.05</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>0.18</td>
<td>0.11</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>0.13</td>
<td>0.16</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.21</td>
<td>0.06</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
<td>-0.23</td>
<td>0.04</td>
</tr>
<tr>
<td>Apo AI, mg/mL</td>
<td>-0.24</td>
<td>0.053</td>
</tr>
<tr>
<td>Apo B, mg/mL</td>
<td>0.08</td>
<td>0.52</td>
</tr>
<tr>
<td>ApoB/ApoAI</td>
<td>0.23</td>
<td>0.06</td>
</tr>
<tr>
<td>Leptin ng/mL</td>
<td>0.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adiponectin μg/mL</td>
<td>-0.71</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| L:A ratio                   | ...| ...
| Resistin, ng/mL             | 0.09| 0.55 |
| IMT, mm                     | 0.36| <0.001 |

Spearman’s rank correlation coefficient (ρ) is shown.

Table 2. Multiple Regression Analysis for Carotid Intima Media Thickness With Clinical Parameters and L:A Ratio

<table>
<thead>
<tr>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.438</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.006</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.199</td>
</tr>
<tr>
<td>Homeostasis model of insulin resistance–revised</td>
<td>0.22</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.032</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.087</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.069</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.015</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>-0.152</td>
</tr>
<tr>
<td>L:A ratio</td>
<td>0.333</td>
</tr>
</tbody>
</table>

β standard regression coefficient.

Results and Discussion

The characteristics of the subjects selected for this study are shown in Table 1. The age ranged between 29 and 78 years; hypertension was present in 23%, dyslipidemia in 35%, and diabetes in 4.6% of subjects.

L:A ratio was significantly correlated to body mass index, waist, hip, waist-to-hip ratio, systolic blood pressure, IMT, high-density lipoprotein, apolipoprotein A-I, glucose, and the homeostasis model of insulin resistance–revised (Table 1). No significant correlation was observed with age, diastolic blood pressure, low-density lipoprotein, triglycerides, apolipoprotein B, ApoB/ApoA-I ratio, insulin, alanine transaminase, γ-glutamyl-transferase, and resistin (Table 1). In addition, when the relationship between IMT and adiponectin or leptin alone was analyzed, only leptin plasma levels were significantly associated with IMT (r=0.301, P<0.01).

We performed multiple regression analysis including in the statistical model the risk factors known to affect IMT (age, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol, triglycerides, total cholesterol, body mass index, glucose, and L:A ratio); we observed that only age, L:A, and glucose were independent predictors of IMT (Table 2); the analysis of variance inflation factors excluded multicollinearity for these variables.

As expected, obese subjects (body mass index >30 kg/m²; n=19; mean age 61±7 years) showed a significantly higher L:A ratio compared with nonobese subjects (1.20 versus 0.42, respectively, P<0.001); in addition, subjects with the metabolic syndrome (n=13, mean age 55±13 years) showed a significantly higher L:A ratio level (0.79) compared with subjects without (0.52; P<0.01).

Our data indicate, for the first time, that the L:A ratio, together with age and glucose, is an independent predictor of IMT in healthy subjects. Of note, when the predictive power on IMT levels of leptin and adiponectin per se was assessed by multiple regression analysis, none of the 2 adipokines appeared to be an independent predictor of IMT, whereas body mass index resulted in an independent predictor of IMT. It is reasonable that the obesity status could influence the levels of adipokines; however, our data suggest that the evaluation of L:A ratio could be a powerful predictor of IMT independent of body mass index not only in patients with diabetes, but also in healthy subjects.
According to our data, the L:A ratio is a powerful marker for predicting IMT thickness and, possibly, cardiovascular outcome. Furthermore, because the levels of the 2 adipokines are more sensitive to metabolic perturbations, the ratio could be of interest to monitor the severity of the metabolic syndrome, in agreement with Inoue et al, who suggested the use of the L:A ratio to assess insulin resistance in subjects without hyperglycemia and Satoh et al, who suggested the use of the L:A ratio as an atherogenic index in obese type 2 diabetes subjects.

In conclusion, we show here that the L:A ratio is a powerful independent predictor of IMT in healthy subjects and correlates with several anthropometric, metabolic, and clinical parameters better than each single adipokine. Further studies are warranted to clarify whether modification of the L:A ratio after lifestyle and/or pharmacological treatment could result in beneficial effects in terms of cardiovascular outcome.

Acknowledgments
The excellent technical support of Ms Paola Assi and Giovanna Micciché is gratefully acknowledged.

Sources of Funding
This work was supported by grants from Università degli Studi di Milano (FIRST) and Ministero dell’Istruzione, dell’Università e della Ricerca (PRIN).

Disclosures
None.

References
Leptin:Adiponectin Ratio Is an Independent Predictor of Intima Media Thickness of the Common Carotid Artery
Giuseppe Danilo Norata, Sara Raselli, Liliana Grigore, Katia Garlaschelli, Elena Dozio, Paolo Magni and Alberico L. Catapano

Stroke. 2007;38:2844-2846; originally published online September 6, 2007;
doi: 10.1161/STROKEAHA.107.485540
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/38/10/2844

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/