Analysis of the Factors Contributing to Serum Retinol Binding Protein and Transthyretin Levels in Japanese Adults

Akihiro Yoshida¹, Yasuko Matsutani², Yoshiko Fukuchi², Kensuke Saito³, and Michitaka Naito²

¹Department of Clinical Laboratory, Nakatsugawa Municipal Hospital, Nakatsugawa, Gifu, Japan.
²Division of Nutrition & Health, School and Graduate School of Life Studies, Sugiyama Jogakuen University, Nagoya, Japan.
³Marketing Division, Dade Behring, Tokyo, Japan.

Objective: We examined various factors possibly related to metabolic syndrome, particularly focusing on nutritional assessment proteins such as retinol binding protein (RBP) and transthyretin (TTR), and remnant lipoproteins.

Materials and Methods: Fasting serum lipid was analyzed in 58 Japanese adult volunteers (33 men and 25 women, 42.5 ± 10.1 years old).

Results: The lipid profiles of the subjects were classified by lipoprotein polyacrylamide gel electrophoretic patterns into Types S (n=10), A (n=37), and N (n=11), according to the method described in Internal Medicine 42: 244, 2003. RBP and TTR were significantly higher in Type N than in Types S and A. In multivariate analysis, RBP was accounted for by remnant-like particle-triglyceride (RLP-TG), interleukin 6, body mass index and low-density lipoprotein (LDL)-cholesterol (adjusted R²=0.621). TTR was accounted for by lipoprotein(a), adiponectin and RLP-TG (adjusted R²=0.415). Malondialdehyde-LDL was significantly accounted for by LDL-cholesterol and RLP-cholesterol (adjusted R²=0.601). Lipoprotein(a) and LDL-cholesterol were independent variables for oxidized LDL antigen (adjusted R²=0.620). High-sensitivity C-reactive protein was accounted for by interleukin 6, immunoreactive insulin and oxidized LDL antigen (adjusted R²=0.361). Uric acid and body mass index were independent variables for adiponectin (adjusted R²=0.429).

Conclusion: RBP and TTR may be useful as convenient and simple clinical markers of overnutrition and possibly of metabolic syndrome.


Key words: Remnant lipoprotein, Retinol binding protein, Overnutrition, Metabolic syndrome

Introduction

Lowering low-density lipoprotein-cholesterol (LDL-C) levels is widely accepted as an effective tool in reducing and preventing coronary heart disease (CHD) progression and cardiac events in hypercholesterolemic and even normocholesterolemic subjects. However, triglyceride (TG) has also been shown as an independent risk factor for cardiovascular disease, even adjusted for high-density lipoprotein-cholesterol (HDL-C). Evidence is accumulating that the risk for CHD can be reduced still further through the combination of LDL-lowering therapy with the modification of other risk factors. One potential secondary target of therapy is metabolic syndrome (MS), which represents a constellation of lipid and nonlipid risk factors of metabolic origin.

The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) Guidelines published in 2001 define MS as a new secondary target for cardiovascular risk reduction therapy beyond LDL-C lowering. One of this publication’s major features is that it identifies persons with multiple metabolic risk factors as candidates for intensified therapeutic lifestyle changes. The atherogenic lipid profile
associated with MS consists of the following: increased apolipoprotein (Apo) B, plasma TG, and intermediate density lipoprotein levels; reduced HDL-C concentration; and smaller, dense, cholesteryl ester-depleted LDL particles.

In a previous study, we classified lipoprotein profiles by polyacrylamide gel electrophoresis (PAGE) and showed that this classification may offer a new clinical tool to make up for the weak points in WHO classification, particularly in relation to the presence of a midband. We also proposed the usefulness of serum total cholesterol (TC)/TG and LDL-C/TG ratios for predicting the presence of small, dense LDL as a simple indicator.

In this study, we examined various factors possibly related to MS, particularly focusing on nutritional assessment proteins such as retinol binding protein (RBP), transthyretin (TTR) and remnant lipoproteins.

Materials and Methods

Subjects
Fifty-eight Japanese volunteers (33 men and 25 women, 42.5 ± 10.1 years old) who visited Nakatsugawa Municipal Hospital for an annual health checkup were enrolled in the study. None of the subjects had a history of cardiovascular disease, diabetes, liver, or renal disease. Blood was drawn from each subject after an overnight fast. All studies were approved by the institutional review board of the hospital, and written consent was obtained from all participants.

Lipoprotein Analysis
Serum TC and TG were determined using enzymatic assay kits (Kyowa Medex, Tokyo, Japan). Apo A-I, A-II, B, C-II, C-III, and E were measured with turbidimetric immunoassay kits (Daichi Chemicals, Tokyo, Japan), and lipoprotein(a) (Lp(a)) with enzyme immunoassay kits (Daichi Chemicals, Tokyo, Japan). Remnant-like particle-cholesterol (RLP-C) and triglyceride (RLP-TG) levels were determined by an immunoadherence method (Japan Immunoresearch Laboratories, Tokyo, Japan).

PAGE of lipoprotein fractions was performed using the LipoPhor system (Joko, Tokyo, Japan) as described previously. The LDL-migration index (LDL-MI) was calculated as described by Mishima et al. as the distance between the very low-density lipoprotein (VLDL) peak and the LDL peak divided by the distance between the VLDL peak and the HDL peak. Lipoprotein profiles were classified into four types (SAND) according to the method described previously: Type S (symmetric), the LDL wave is sharp and is symmetrical to the perpendicular line from the LDL peak to the baseline; Type A (asymmetric), the LDL wave is asymmetric with a broad foot on the cathodic side; Type N (nodular), a nodule is observed on the shoulder of the LDL wave; and Type D (disrupted), continuous components are observed between LDL and VLDL waves with no clear LDL wave.

Retinol Binding Protein (RBP) and Transthyretin (TTR)
Levels of RBP, which has a half-life of about 12 hours, and TTR (also known as prealbumin), which has a half-life of 2 days, were determined by an immunonephrometric procedure (Dade Behring, Tokyo).

Other Materials
Other materials used in this study were obtained as follows: fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) from Arkray (Kyoto); immunoreactive insulin (IRI) from Eiken Chemical (Tokyo); uric acid (UA) from Kyowa Medex (Tokyo); high-sensitivity C-reactive protein (HS-CRP) from Dade Behring (Tokyo); interleukin 6 (IL6) from Fujirebio (Tokyo); leptin (Lep) from BioVendor Laboratory Medicine (Tokyo); adiponectin (AN) from Otsuka Pharmaceutical (Tokyo); anti-oxidized LDL antibody (OxLDLAb) and OxLAB from Biomedica (Vienna); oxidized LDL antigen (OxLDLAg) and MX kit from Kyowa Medex (Tokyo); and malondialdehyde-modified LDL (MDA-LDL) and sandwich ELISA using a monoclonal anti-MDA-LDL antibody (ML25) from Daichi Chemicals (Tokyo).

Insulin resistance was calculated using a homeostasis model assessment: insulin resistance (HOMA-IR). Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m²). Pulse wave velocity (PWV) and ankle-brachial pressure index (ABI) were measured using Vasera VS-1000 (Fukuda Densi, Tokyo). Systolic blood pressure (SBP), diastolic blood pressure (DBP), right (R-) and left (L-) ankle-brachial pressure index (ABI), and right (R-) and brachial (B-) PWV were determined.

Statistical Analysis
Statistical analysis was performed with one-way ANOVA, using StatView, ver. 5.0 (SAS Institute, USA). The results are expressed as the means ± SD. A level of p < 0.05 was considered significant. Univariate regression analysis was performed using linear regression and Pearson’s correlation coefficient, considering R < −0.4 or R > 0.4 to be of significance. Multivariate analysis was performed using stepwise regression analysis.
Table 1. Characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>33</td>
<td>25</td>
<td>58</td>
</tr>
<tr>
<td>Age</td>
<td>39.8 ± 8.5</td>
<td>46.1 ± 11.1</td>
<td>42.5 ± 10.1</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>205.9 ± 37.0</td>
<td>213.4 ± 36.4</td>
<td>209.2 ± 36.5</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>168.9 ± 151.8</td>
<td>127.2 ± 131.8</td>
<td>150.9 ± 143.8</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>56.5 ± 15.7</td>
<td>65.0 ± 13.2*</td>
<td>60.1 ± 15.2</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>123.2 ± 32.2</td>
<td>124.6 ± 31.4</td>
<td>123.8 ± 31.6</td>
</tr>
<tr>
<td>ApoA-I (mg/dL)</td>
<td>136.8 ± 19.7</td>
<td>145.7 ± 15.2</td>
<td>140.7 ± 18.3</td>
</tr>
<tr>
<td>ApoA-II (mg/dL)</td>
<td>30.6 ± 3.4</td>
<td>28.9 ± 4.5</td>
<td>29.8 ± 4.0</td>
</tr>
<tr>
<td>ApoB (mg/dL)</td>
<td>96.0 ± 24.6</td>
<td>97.4 ± 25.3</td>
<td>96.6 ± 24.7</td>
</tr>
<tr>
<td>ApoC-II (mg/dL)</td>
<td>4.2 ± 2.6</td>
<td>3.7 ± 2.6</td>
<td>4.0 ± 2.6</td>
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<tr>
<td>ApoC-III (mg/dL)</td>
<td>10.3 ± 3.9</td>
<td>9.8 ± 3.7</td>
<td>10.1 ± 3.8</td>
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<tr>
<td>ApoE (mg/dL)</td>
<td>4.7 ± 1.6</td>
<td>4.8 ± 1.5</td>
<td>4.8 ± 1.5</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)</td>
<td>14.0 ± 20.0</td>
<td>15.0 ± 16.1</td>
<td>14.4 ± 18.3</td>
</tr>
<tr>
<td>RLP-C (mg/dL)</td>
<td>16.2 ± 12.8</td>
<td>13.1 ± 12.0</td>
<td>14.9 ± 12.4</td>
</tr>
<tr>
<td>RLP-TG (mg/dL)</td>
<td>66.8 ± 117.3</td>
<td>36.7 ± 76.3</td>
<td>53.8 ± 102.0</td>
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<tr>
<td>OxlDLAbs (mU/mL)</td>
<td>1304.4 ± 4095.6</td>
<td>810.4 ± 2112.2</td>
<td>1091.5 ± 3369.9</td>
</tr>
<tr>
<td>OxlLDLAg (U/mL)</td>
<td>9.2 ± 4.6</td>
<td>9.2 ± 4.9</td>
<td>9.2 ± 4.7</td>
</tr>
<tr>
<td>MDA-LDL (U/L)</td>
<td>110.9 ± 40.5</td>
<td>111.6 ± 42.9</td>
<td>111.2 ± 41.2</td>
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<tr>
<td>TC/TG</td>
<td>1.93 ± 0.99</td>
<td>2.41 ± 1.08</td>
<td>2.14 ± 1.10</td>
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<tr>
<td>LDL-C/ApoB</td>
<td>1.30 ± 0.19</td>
<td>1.29 ± 0.16</td>
<td>1.30 ± 0.18</td>
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<tr>
<td>LDL-MI</td>
<td>0.33 ± 0.04</td>
<td>0.34 ± 0.04</td>
<td>0.34 ± 0.04</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>101.2 ± 23.4</td>
<td>97.6 ± 15.9</td>
<td>99.7 ± 20.4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.2 ± 0.8</td>
<td>5.2 ± 0.7</td>
<td>5.2 ± 0.8</td>
</tr>
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<td>IRI (μU/mL)</td>
<td>9.90 ± 4.56</td>
<td>8.91 ± 4.60</td>
<td>9.48 ± 4.56</td>
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<td>HOMA-IR</td>
<td>2.47 ± 1.17</td>
<td>2.25 ± 1.44</td>
<td>2.37 ± 1.29</td>
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<tr>
<td>UA (mg/dL)</td>
<td>5.7 ± 1.1</td>
<td>4.5 ± 1.1***</td>
<td>5.2 ± 1.3</td>
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<td>HsCRP (mg/dL)</td>
<td>0.10 ± 0.11</td>
<td>0.28 ± 1.05</td>
<td>0.17 ± 0.69</td>
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<td>RBP (mg/dL)</td>
<td>4.7 ± 2.4</td>
<td>3.4 ± 1.3*</td>
<td>4.1 ± 2.1</td>
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<tr>
<td>TTR (mg/dL)</td>
<td>32.2 ± 6.9</td>
<td>25.7 ± 6.6**</td>
<td>29.4 ± 7.5</td>
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<tr>
<td>IL-6 (pg/mL)</td>
<td>1.56 ± 1.08</td>
<td>1.68 ± 1.50</td>
<td>1.61 ± 1.27</td>
</tr>
<tr>
<td>Lep (ng/mL)</td>
<td>7.6 ± 12.8</td>
<td>14.1 ± 12.6</td>
<td>10.4 ± 13.0</td>
</tr>
<tr>
<td>AN (ng/mL)</td>
<td>0.84 ± 0.44</td>
<td>1.28 ± 0.70*</td>
<td>1.03 ± 0.60</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8 ± 2.0</td>
<td>23.5 ± 4.1</td>
<td>23.7 ± 3.0</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>126.5 ± 11.4</td>
<td>127.2 ± 21.7</td>
<td>126.8 ± 16.5</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.9 ± 7.8</td>
<td>81.9 ± 14.0</td>
<td>81.9 ± 10.8</td>
</tr>
<tr>
<td>R-ABI</td>
<td>1.16 ± 0.06</td>
<td>1.14 ± 0.05</td>
<td>1.15 ± 0.06</td>
</tr>
<tr>
<td>L-ABI</td>
<td>1.16 ± 0.06</td>
<td>1.15 ± 0.06</td>
<td>1.16 ± 0.06</td>
</tr>
<tr>
<td>R-PWV (m/sec)</td>
<td>12.4 ± 1.4</td>
<td>12.6 ± 2.0</td>
<td>12.5 ± 1.7</td>
</tr>
<tr>
<td>L-PWV (m/sec)</td>
<td>12.5 ± 2.0</td>
<td>12.7 ± 2.0</td>
<td>12.6 ± 2.0</td>
</tr>
<tr>
<td>B-PWV (m/sec)</td>
<td>6.2 ± 0.9</td>
<td>6.1 ± 1.3</td>
<td>6.2 ± 1.1</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01, ***p < 0.0001, Men vs Women

Results

The lipid profiles of the subjects are summarized in Table 1. They were classified by the lipoprotein PAGE pattern into Types S (n = 10), A (n = 37), and N (n = 11). No subjects showed the Type D pattern. The relationship between SAND classifications and lipid profiles is shown in Table 2. Serum TC was not different among the three types, but LDL-C was slightly higher in Type A than in Type S. HDL-C significantly decreased from Type S to Type N. Serum TG tended to increase from Type S to Type N. ApoB was higher in Type A and N compared with Type S. ApoC-II, C-III and E were higher in Type N than in Types S and A.
The TC/TG ratio significantly decreased from Type S to Type N. LDL-MI was significantly higher, and LDL-C/ApoB was significantly lower, in Type N than in Types S and A. The tendencies in the lipid profiles observed in this study are consistent with the results we previously reported. RBP and TTR were significantly higher in Type N than in Types S and A. MDA-LDL significantly increased from Type S to Type N.

In univariate analysis, a strong positive correlation was observed between RBP and logTG, ApoC-II, C-III, E, logRLP-C, and logRLP-TG (Table 3). There was a negative correlation between RBP and HDL-C. There was also a negative correlation between RBP and TC/TG and LDL-C/ApoB, and a positive correlation

### Table 2. Characteristics of study subjects according to the SAND classification

<table>
<thead>
<tr>
<th>SAND Classification</th>
<th>S</th>
<th>A</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>37</td>
<td>11</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>185.9 ± 32.6</td>
<td>214.4 ± 36.4</td>
<td>212.5 ± 35.5</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>58.1 ± 18.0</td>
<td>138.2 ± 122.6</td>
<td>278.2 ± 191.1 *** **</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>78.8 ± 15.0</td>
<td>58.4 ± 11.4 ***</td>
<td>49.0 ± 12.1 *** **</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>101.5 ± 30.6</td>
<td>132.3 ± 29.3 **</td>
<td>115.7 ± 30.2</td>
</tr>
<tr>
<td>ApoA-I (mg/dL)</td>
<td>150.8 ± 24.3</td>
<td>139.3 ± 16.2</td>
<td>135.9 ± 17.3</td>
</tr>
<tr>
<td>ApoA-II (mg/dL)</td>
<td>30.3 ± 5.6</td>
<td>29.4 ± 2.9</td>
<td>30.8 ± 5.5</td>
</tr>
<tr>
<td>ApoB (mg/dL)</td>
<td>74.1 ± 20.7</td>
<td>100.6 ± 24.5 **</td>
<td>103.5 ± 17.4 **</td>
</tr>
<tr>
<td>ApoC-II (mg/dL)</td>
<td>2.1 ± 1.4</td>
<td>3.7 ± 2.3 *</td>
<td>6.6 ± 2.6 *** **</td>
</tr>
<tr>
<td>ApoC-III (mg/dL)</td>
<td>7.5 ± 2.2</td>
<td>9.3 ± 2.8</td>
<td>15.1 ± 3.8 *** ***</td>
</tr>
<tr>
<td>ApoE (mg/dL)</td>
<td>4.5 ± 1.3</td>
<td>4.4 ± 1.3</td>
<td>6.2 ± 1.8 ** **</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)</td>
<td>23.7 ± 32.3</td>
<td>14.2 ± 6.6</td>
<td>14.2 ± 14.8</td>
</tr>
<tr>
<td>RLP-C (mg/dL)</td>
<td>8.7 ± 4.7</td>
<td>13.5 ± 10.9</td>
<td>24.9 ± 16.7 ** **</td>
</tr>
<tr>
<td>RLP-TG (mg/dL)</td>
<td>13.9 ± 12.9</td>
<td>45.9 ± 98.6</td>
<td>116.8 ± 134.2 ** **</td>
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<tr>
<td>OxLDLAb (mU/mL)</td>
<td>1447.6 ± 3150.1</td>
<td>1207.9 ± 3906.8</td>
<td>376.0 ± 336.1</td>
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<tr>
<td>OxLDLAg (U/mL)</td>
<td>10.4 ± 0.6</td>
<td>9.5 ± 4.7</td>
<td>7.0 ± 1.8</td>
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<tr>
<td>MDA-LDL (U/L)</td>
<td>75.6 ± 25.9</td>
<td>111.6 ± 40.4 **</td>
<td>142.3 ± 29.3 **</td>
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<tr>
<td>TC/TG</td>
<td>3.42 ± 0.95</td>
<td>2.12 ± 0.90 ***</td>
<td>1.07 ± 0.58 *** **</td>
</tr>
<tr>
<td>LDL-C/ApoB</td>
<td>1.36 ± 0.07</td>
<td>1.33 ± 0.13</td>
<td>1.12 ± 0.28 ** **</td>
</tr>
<tr>
<td>LDL-MI</td>
<td>0.31 ± 0.02</td>
<td>0.33 ± 0.03</td>
<td>0.39 ± 0.03 ** ** **</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>93.8 ± 6.1</td>
<td>100.5 ± 24.4</td>
<td>102.3 ± 12.3</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.1 ± 0.7</td>
<td>5.2 ± 1.8</td>
<td>5.6 ± 0.6</td>
</tr>
<tr>
<td>IRI (µU/mL)</td>
<td>9.27 ± 3.70</td>
<td>9.02 ± 5.02</td>
<td>11.19 ± 3.42</td>
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<tr>
<td>HOMA-IR</td>
<td>2.17 ± 0.99</td>
<td>2.28 ± 1.41</td>
<td>2.86 ± 1.05</td>
</tr>
<tr>
<td>UA (mg/dL)</td>
<td>4.9 ± 1.1</td>
<td>5.1 ± 1.2</td>
<td>5.8 ± 1.5</td>
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<tr>
<td>HS-CRP (mg/dL)</td>
<td>0.60 ± 1.65</td>
<td>0.08 ± 0.09</td>
<td>0.10 ± 0.14</td>
</tr>
<tr>
<td>RBP (mg/dL)</td>
<td>3.0 ± 0.9</td>
<td>3.9 ± 1.7</td>
<td>5.8 ± 3.0 ** **</td>
</tr>
<tr>
<td>TTR (mg/dL)</td>
<td>25.0 ± 5.6</td>
<td>28.7 ± 6.0</td>
<td>35.8 ± 9.6 ** **</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>2.27 ± 2.22</td>
<td>1.56 ± 1.05</td>
<td>1.21 ± 0.37</td>
</tr>
<tr>
<td>Lep (ng/mL)</td>
<td>11.8 ± 17.3</td>
<td>10.2 ± 13.0</td>
<td>10.1 ± 9.3</td>
</tr>
<tr>
<td>AN (ng/mL)</td>
<td>1.15 ± 0.54</td>
<td>1.08 ± 0.61</td>
<td>0.76 ± 0.57</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.8 ± 3.8</td>
<td>23.8 ± 2.9</td>
<td>24.0 ± 2.8</td>
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<tr>
<td>SBP (mmHg)</td>
<td>122.9 ± 19.0</td>
<td>125.9 ± 13.8</td>
<td>133.4 ± 21.7</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.5 ± 11.8</td>
<td>81.7 ± 10.2</td>
<td>85.9 ± 11.5</td>
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<tr>
<td>R-ABI</td>
<td>1.17 ± 0.04</td>
<td>1.15 ± 0.06</td>
<td>1.15 ± 0.06</td>
</tr>
<tr>
<td>L-ABI</td>
<td>1.17 ± 0.06</td>
<td>1.15 ± 0.07</td>
<td>1.17 ± 0.04</td>
</tr>
<tr>
<td>R-PWV (m/sec)</td>
<td>12.1 ± 1.8</td>
<td>12.5 ± 1.7</td>
<td>12.9 ± 1.6</td>
</tr>
<tr>
<td>L-PWV (m/sec)</td>
<td>12.2 ± 1.8</td>
<td>12.5 ± 2.1</td>
<td>13.1 ± 1.9</td>
</tr>
<tr>
<td>B-PWV (m/sec)</td>
<td>5.4 ± 1.0</td>
<td>6.3 ± 0.9 *</td>
<td>6.5 ± 1.3 *</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.0001 compared with Type S.

### Notes

1. MDA-LDL: Malondialdehyde-LDL
2. OxLDLAb: Oxidized-LDL activity
3. OxLDLAg: Oxidized-LDL antigen
4. TC/TG: Total Cholesterol to Triglycerides ratio
5. HDL-C: High-Density Lipoprotein Cholesterol
6. LDL-C: Low-Density Lipoprotein Cholesterol
8. ApoA-II: Apolipoprotein A-II
9. ApoB: Apolipoprotein B
10. ApoC: Apolipoprotein C
11. ApoE: Apolipoprotein E
12. Lp(a): Lipoprotein(a)
13. RLP: Remnant-like Particle
14. FPG: Fasting Plasma Glucose
15. HbA1c: Hemoglobin A1c
16. IRI: Insulin Resistance Index
17. HOMA-IR: Homeostasis Model Assessment-Insulin Resistance
18. UA: Uric Acid
19. HS-CRP: High-Sensitivity C-Reactive Protein
20. RBP: Retinol Binding Protein
21. TTR: Transthyretin
22. IL-6: Interleukin-6
23. Lep: Leptin
24. AN: Albumin
25. BMI: Body Mass Index
26. SBP: Systolic Blood Pressure
27. DBP: Diastolic Blood Pressure
28. R-ABI: Right-Artery Brachial Artery Index
29. L-ABI: Left-Artery Brachial Artery Index
30. R-PWV: Right-Pulse Wave Velocity
31. L-PWV: Left-Pulse Wave Velocity
32. B-PWV: Brachial-Pulse Wave Velocity
between RBP and LDL-MI. There was no significant correlation between RBP and BMI.

There was a positive correlation between TTR and logTG, ApoC-II, C-III, logRLP-C and logRLP-TG. There was also a negative correlation between TTR and TC/TG, and a positive correlation between TTR and LDL-MI. There was no significant correlation between TTR and BMI.

Multivariate analysis was performed by a forward stepwise regression procedure, using HDL-C, LDL-C, logLp(a), logRLP-C, logRLP-TG, MDA-LDL, logOxLDLAg, logFPG, HbA1c, IRI, UA, RBP, TTR, logHsCRP, logIL-6, logLeptin, BMI and AN as independent variables (Table 4).

RBP was accounted for by logRLP-TG (0.560), TTR (0.363), and LDL-C (-0.185) (adjusted R² = 0.646). TTR was accounted for by RBP (0.541), UA (0.247), and logLp(a) (-0.203) (adjusted R² = 0.527). Analysis was also performed by excluding RBP and TTR from the independent variables. In this case, RBP was accounted for by logRLP-TG (0.867), logIL-6 (0.288), BMI (-0.251), and LDL-C (-0.199) (adjusted R² = 0.621). TTR was accounted for by logLp(a) (-0.378), AN (-0.315), and logRLP-TG (0.309) (adjusted R² = 0.415)

MDA-LDL was accounted for by LDL-C (0.566) and logRLP-C (0.405) (R² = 0.717). logLp(a) (0.793) and LDL-C (0.183) were independent variables for logOxLDLAg (R² = 0.620). logHsCRP was accounted for by logIL-6 (0.354), IRI (0.253), and logOxLDLAg (0.254) (R² = 0.361). UA (-0.517) and BMI (-0.304) were independent variables for AN (R² = 0.429).

**Discussion**

RBP and TTR have been used clinically as rapid turnover proteins for assessing the short-term fluctuation of nutritional states. RBP is the only specific transport protein for retinol (vitamin A) in the circulation. Although hepatocytes are regarded as the principal source of circulating RBP, adipocytes have the second-highest expression level, indicating that they may be involved in retinoid storage and metabolism. RBP is easily filtered through the renal glomerular membrane and binds TTR to form a complex that prevents renal clearance. The only known function of RBP has been to deliver retinol to tissues; however, very recently, Yang et al. reported that serum RBP levels were elevated in insulin-resistant mice and also in humans with obesity and type 2 diabetes. Serum RBP levels were increased in obese-non-diabetic and obese-diabetic subjects compared with lean controls; however, there was no difference in the magnitude of serum RBP elevation between the obese and obese-diabetic groups, suggesting that obesity and insulin resistance are associated with elevated RBP. These results suggest that RBP and TTR may be related to the pathophysiology.

**Table 3. Correlation of RBP and TTR with other variables**

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<tr>
<td>RBP</td>
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ology of MS or remnant lipoprotein metabolism. Interestingly, there was no or only a weak correlation between RBP or TTR and BMI, suggesting that the increase of these proteins may not be a simple result of obesity. RLP-TG was shown to be an independent variable for RBP. By the SAND classification, RBP and TTR are significantly higher in Type N than in Types S and A, suggesting that these proteins are related to lipoproteins, particularly remnant lipoproteins. To our knowledge, the detailed relation between these proteins and MS has never been reported.

AN, an adipose-specific secretory protein, exhibits antidiabetic and antiatherogenic properties. Plasma AN concentrations have been reported to be significantly lower in men than in women, but were not different between pre- and postmenopausal women, suggesting that androgen-induced hypoadiponectinemia may be related to a high risk of insulin resistance and atherosclerosis in men. Plasma concentrations of AN have also been shown to be significantly lower in obese subjects than in non-obese subjects. Interestingly, these results showed a significant negative correlation between AN and UA. The precise mechanism is not clear, but the increase of UA may be a response to oxidative stress. In the hypoadiponectinemic state, in vivo oxidative stress may be increased. Plasma AN concentrations have been reported to be correlated negatively with waist circumference, visceral fat area, serum TG concentration, FPG, fasting plasma insulin, SBP and DBP in both sexes. Hypoadiponectinemia has been closely associated with the clinical phenotype of MS, using the criteria for Japanese people.

OxLDLAg, a marker of modified LDL, was mainly accounted for by Lp(a) and LDL-C, suggesting that the concentration of OxLDLAg may be mainly determined by Lp(a) and LDL-C; however, MDA-LDL, another marker of modified LDL, was significantly related with LDL-C and RLP-C. Further analysis will be needed to clarify the determinants of oxidative modification of LDL.

MS is quite common among the US population, and to a lesser extent, among the Japanese. The age-adjusted prevalence of MS among the US population as defined by NCEP-ATPⅢ was calculated as 23.7%. Another study showed that 44% of the US population over 50 years of age meets the NCEP criteria. MS is very common even in Japan, and affects 24.4% of the Japanese male population aged 60 ± 12 years, when using the criteria of an 85 cm abdominal circumference (instead of the 102 cm proposed by NCEP-ATPⅢ) recommended by the joint committee for the guideline of obesity and MS in Japan. In addition to genetic predisposition, MS is clearly associated with overeating and lack of exercise. It is urgent to clarify the pathophysiology of MS in order to prevent early death and disability caused by MS-related outcomes such as myocardial infarction. In this study, we found that

<table>
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<th>Table 4. Multivariate regression analysis</th>
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RBP and TTR may be new markers of overnutrition, and possibly of MS. It is necessary to study the relationship between these proteins and MS in greater detail.

Acknowledgement

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References


