Insulin Resistance Is Unrelated to Circulating Retinol Binding Protein and Protein C Inhibitor

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Objective: The objective of this study was to investigate the association of insulin resistance with RBP factors and PCI active antigen.

Design and Setting: This was a clinical study.

Patients: Nondiabetic humans with high (IS; n = 20, 14 females, six males, aged 47.2 ± 1.9 yr, body mass index 26 ± 1 kg/m2) and low (IR; n = 20, 14 females, six males, aged 45.5 ± 1.7 yr, body mass index 28 ± 1 kg/m2) insulin-stimulated glucose-disposal (M) participated in this study.

Main Outcome Measures: M was measured by 2-h hyperinsulinem-mic (40 mU·min⁻¹·m⁻²)-isoglycemic clamp tests. Measurements of RBP were performed using a nephelometric method and validated using quantitative Western blotting.

Results: M (80–120 min) was higher in IS (10.9 ± 0.6 mg·min⁻¹·kg⁻¹) than IR (4.0 ± 0.2; P < 10⁻¹²). Fasting plasma RBP concentrations were comparable between IS and IR measured by both nephelometry (IS: 4.4 ± 0.3; IR: 4.6 ± 0.3 ng/ml, P = 0.6) and quantitative Western blot (IS 7.9 ± 0.5, IR 8.3 ± 0.6 ng/ml, P = 0.6). Fasting plasma PCI active antigen was similar in both groups. Plasma RBP and PCI were not significantly related to M. RBP was positively correlated with uric acid (r = 0.488, P = 0.003), triglycerides (r = 0.592, P < 0.001), prealbumin (r = 0.63, P < 0.0001), and vitamin A (r = 0.75, P < 10⁻⁶).

Conclusions: Our data demonstrate that healthy, insulin-resistant humans do not show altered plasma retinol binding factors, such as RBP and PCI. Both do not significantly correlate with insulin sensitivity. Thus, our findings do not support the hypothesis of insulin sensitivity modulation by proteins involved in retinol transport.

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active antigen, might interfere with whole-body insulin sensitivity in nondiabetic humans. To exclude direct effects of body weight, age, and gender on insulin resistance, we compared insulin-sensitive and -resistant humans that were well matched for age, BMI, and gender.

### Subjects and Methods

#### Study participants

Forty nondiabetic humans were recruited by local advertising (Table 1). The subjects were healthy and not treated with medications for diabetes, hypertension, or dyslipidemia or other medication known to influence glucose homeostasis. None of the women were taking oral contraceptives, eight women were postmenopausal, and one woman was receiving postmenopausal estrogen therapy. All participants had been instructed to refrain from excessive physical exercise and ingest an isocaloric carbohydrate-rich diet 3 d before the examinations. The protocol was approved by the institutional ethics board, and all study participants gave informed consent after the nature and the possible consequences of the procedures had been explained.

#### Study d 1

After a 12-h overnight fast, study participants underwent a complete medical history, taken with routine laboratory, physical check, and blood sampling for measurement of RBP and PCI. Urinary protein excretion was measured by Multistix 10 SG (Bayer, Newbury, UK) and was negative in all subjects. Body weight and fat mass were measured by Tanita bioimpedance balance (Yveline, UK). Thereafter an oral glucose (75 g) tolerance test (OGTT) was performed.

#### Study d 2

After a 12-h overnight fast, two catheters (Vasofix; Braun, Melsungen, Germany) were inserted in the left and right antecubital vein for blood sampling and infusions, respectively. In 21 subjects, a primed-continuous infusion (5 min: 4 mg/kg lean body weight; 0.04 mg/min per lean body weight) of n-[6,6-H]glucose (98% enriched; Cambridge Isotope Laboratories, Andover, MA) was started at −120 min for measurement of endogenous glucose production (EGP) (22). The clamp goal was determined from the mean of three basal plasma glucose measurements.

### TABLE 1. Anthropometric and clinical characteristics including (serum) routine laboratory measurements of the IS and IR study participants

<table>
<thead>
<tr>
<th></th>
<th>IS</th>
<th>IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.2 ± 1.9</td>
<td>45.5 ± 1.7</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>14/6</td>
<td>14/6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 ± 0.8</td>
<td>27.9 ± 1.1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74.7 ± 2.8</td>
<td>80.5 ± 3.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.7 ± 2.0</td>
<td>169.6 ± 2.2</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.85 ± 0.02</td>
<td>0.90 ± 0.02</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>21.5 ± 1.9</td>
<td>27.0 ± 2.2</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>53.2 ± 2.8</td>
<td>53.6 ± 2.9</td>
</tr>
<tr>
<td>RR syst/dia (mm Hg)</td>
<td>119 ± 3.78 ± 2</td>
<td>121 ± 3.79 ± 1</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.5 ± 0.1</td>
<td>5.7 ± 0.1</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>90.0 ± 7.3</td>
<td>103.5 ± 14.8</td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dl)</td>
<td>220.0 ± 7.6</td>
<td>209.8 ± 7.8</td>
</tr>
<tr>
<td>Serum LDL cholesterol (mg/dl)</td>
<td>65.2 ± 2.7</td>
<td>55.7 ± 2.4</td>
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<tr>
<td>Serum LDL cholesterol (mg/dl)</td>
<td>136.7 ± 7.6</td>
<td>133.7 ± 7.7</td>
</tr>
<tr>
<td>ASAT (U/liter)</td>
<td>24.0 ± 1.5</td>
<td>24.4 ± 2.2</td>
</tr>
<tr>
<td>ALAT (U/liter)</td>
<td>21.5 ± 1.5</td>
<td>26.5 ± 4.5</td>
</tr>
<tr>
<td>gGT (U/liter)</td>
<td>15.0 ± 1.1</td>
<td>22.1 ± 3.1</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.90 ± 0.03</td>
<td>0.80 ± 0.04</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>4.6 ± 0.2</td>
<td>4.8 ± 0.2</td>
</tr>
</tbody>
</table>

Student’s t test IS vs. IR. ASAT, Aspartate aminotransaminase; ALAT, alanine aminotransaminase; RR syst/dia, systolic and diastolic blood pressure; HbA1c, hemoglobin A1c.

Whenever the calculated clamp goal was outside 80 and 100 mg/dl, 80 and 100 mg/dl, respectively, were taken as the clamp goal. The hyperinsulinemic-isoglycemic clamp test was started with primed-continuous insulin (Actrapid; Novo Nordisk, Bagsværd, Denmark) infusion (40 mU insulin per minute per square meter body surface area). Plasma glucose was maintained at the clamp goal by infusing variable amounts of n-glucose, enriched with n-[6,6-H]glucose. Blood was collected in EDTA-containing tubes, centrifuged, and plasma was stored at −20°C.

According to the insulin-stimulated glucose use, we divided the participants into two groups, an insulin-resistant (IR); insulin-mediated glucose uptake (M value) of 5.1 mg/kg/min or below) and an insulin-sensitive (IS; M value > 5.1 mg/kg/min) group (Table 1).

### Plasma metabolites and proteins

Plasma concentrations of glucose, insulin, C-peptide, and free fatty acids (FFAs) were measured as described (23, 24). Serum concentrations of triglycerides and total and high-density lipoprotein (HDL) cholesterol were measured by routine laboratory techniques (www.kimcl.at).

Plasma RBP concentration was measured by three independent methods: nephelometry, ELISA, and quantitative Western blot. For measurement of RBP by nephelometry, N Antiserum to human plasma RBP (code OUVO; Dade Behring Inc., Deerfield, IL) was used. Measurements were done with the Dade Behring nephelometer BN II. Intra- and interassay coefficients of variation were 1.9 and 2.2%, respectively. The assay was approved for in vitro diagnostic use in the United States and Europe and demonstrated to show excellent correlations with results obtained from radial immunodiffusion.

Because the majority of previous publications analyzed RBP in serum (8, 13), we also measured RBP in serum and plasma in 15 humans by using the nephelometric method. RBP in plasma (2.9 ± 0.4 mg/dl) was not different from that in serum (3.2 ± 0.4 mg/dl) (P = 0.6), and serum and plasma values closely correlated with each other (r = 0.996, P < 10−12).

For the determination of RBP by quantitative Western blotting, we precisely followed detailed protocols published by Graham et al. (25). In brief, full-length recombinant human RBP4 (AdipoGen, Seoul, South Korea) was used to prepare two different series of RBP4 standard solutions: 1, 0.5, 0.25, and 0.13 and 0.63, 0.31, 0.16, and 0.12 µg/ml, respectively. Sera were diluted 1:200 or 1:400, separated by SDS-PAGE and transferred onto a polyvinylidene difluoride membrane (GE Healthcare Biosciences, Munich, Germany). After blocking nonspecific binding, blots were incubated overnight at 4°C with a polyclonal rabbit anti-human RBP4 antibody (Dako Cytomation, Hamburg, Germany) followed by 1-h incubation at room temperature with horseradish peroxidasen conjugated donkey anti-rabbit IgG secondary antibody (GE Healthcare Biosciences). Chemiluminescence generated by the ECL Plus Western blotting detection system (GE Healthcare Biosciences) was detected and quantified using the Lumi-Imager F1 and the Lumi Analyst 3.0 software, respectively (Roche Diagnostics, Mannheim, Germany). Second-order polynomial curves were used to fit the purified RBP4 standards (range r² = 0.9747–0.9934; mean r² = 0.9873) for each individual gel and calculate concentrations in serum samples. Samples exceeding upper or lower limits of the standard curve were rerun at appropriate dilutions.

The RBP-ELISA was performed following the detailed instructions of the manufacturer (AdipoGen Inc., Seoul, South Korea).

Unless otherwise noted, all statements in this article refer to results obtained by the nephelometric method.

Because RBP concentrations are also governed by vitamin A status and the carrier protein prealbumin, vitamin A in plasma was measured using a commercially available, Communauté Européenne-marked HPLC assay (Chromsystems, Munich, Germany), and prealbumin in plasma was determined by nephelometry (Dade Behring; catalog no. OUIF). Plasma PCI active antigen was measured with PCI Actibind ELISA kit (Technoclone, Vienna, Austria) and is given as percent of normal human plasma.

### Gas chromatography/mass spectrometry

Mole percent excess of plasma and infused n-[6,6-H]glucose was measured by gas-chromatography/mass spectrometry as described (1).
Calculations

EGP and M values, both given in milligrams glucose per minute per kilogram, were calculated as described (24, 26, 27). Hepatic insulin resistance index was calculated by multiplying fasting insulin concentrations with fasting EGP as described by Gastaldelli et al. (28). OGTT-based index of insulin sensitivity (OGIS) was determined from OGTT plasma glucose/insulin concentrations as described (29).

Statistical analyses

All data are given as means ± se. Comparisons within each group were analyzed with the two-tailed paired Student’s t test. Comparisons between both groups were done with the two-tailed unpaired Student’s t test. Linear correlations are Pearson product-moment correlations. Differences were considered statistically significant at \( P < 0.05 \).

Results

Participants’ characteristics

The anthropometric and clinical characteristics of the IS and IR participants are given in Table 1. The groups were matched for age, gender, and BMI. HDL cholesterol was higher in IS, whereas γ-glutamyl transferase (γGT) was elevated in IR (each \( P < 0.05 \)). Plasma vitamin A concentrations were comparable between IS and IR study participants (IS: 2.9 ± 0.2; IR: 2.8 ± 0.2 μmol/liter; \( P = 0.7 \)). Plasma vitamin A concentrations were associated with fasting RBP concentrations (\( r = 0.75; P < 10^{-9} \)). Plasma prealbumin which carries RBP in the circulation was not different between the groups (IS: 25.7 ± 0.2; IR: 24.9 ± 0.2 mg/dl; \( P = 0.6 \)) and was positively correlated to fasting RBP concentrations (\( r = 0.63; P < 10^{-4} \)).

OGTT (Fig. 1)

During the OGTT, plasma glucose between 30 and 120 min, plasma insulin between 20 and 150 min, and FFAs between 60 and 90 min were higher in IR (each \( P < 0.05 \) vs. IS) (Fig. 1, A–C).

IS, when determined from the OGTT (OGIS), was lower in IR at 120 min (397 ± 16 ml/min⁻¹·m⁻² vs. IS: 448 ± 13, \( P < 0.02 \)) and 180 min (411 ± 17 ml/min⁻¹·m⁻² vs. IS: 455 ± 10, \( P < 0.04 \)).

RBP during OGTT. Plasma RBP concentrations were not different between both groups before and 90 and 180 min after glucose load (Fig. 1D). At 180 min, IS showed lower plasma RBP when compared with basal values (Fig. 1D) (\( P < 0.03 \)). RBP values were lower in females (3.7 ± 0.2 mg/dl) than males before (5.8 ± 0.5 mg/dl, \( P < 0.001 \)) and 90 (3.6 ± 0.2 vs. 5.1 ± 0.2 mg/dl, \( P < 0.001 \)) and 180 min (3.6 ± 0.2 vs. 5.0 ± 0.3 mg/dl, \( P = 0.002 \)) after ingestion of glucose.

Clamp test

Metabolites and hormones. During the clamp tests, plasma glucose was different only between 20 and 50 min (\( P < 0.05 \)) (Fig. 2A). Clamp insulin infusion resulted in a similar increase in plasma insulin in both groups (Fig. 2B). During clamp, plasma FFAs were up to 195% higher in IR between 60 and 120 min (\( P < 0.001 \)) (Fig. 2C).

Glucose metabolism. During standardized hyperinsulinemia, whole-body glucose use [M (80–120 min)] was lower in IR (4.0 ± 0.2 mg glucose per minute per kilogram) when compared with IS (10.9 ± 0.6; \( P < 10^{-12} \)) (Fig. 2D). EGP was comparable before and during the clamp in both groups (Fig. 2E). Hepatic insulin resistance index tended to be higher in IR (13.3 ± 2.3), compared with IS (8.2 ± 0.9; \( P = 0.059 \)).

RBP during clamp. Fasting levels of plasma RBP were not different between IS and IR (IS: 4.4 ± 0.3; IR: 4.6 ± 0.3 mg/dl) (Fig. 2F). Moreover, plasma RBP was comparable between...
both groups during the clamp test (Fig. 2F). After 90 min hyperinsulinemia, plasma RBP decreased by 9 and 7% in IS and IR, respectively (P < 0.005) (Fig. 2F). RBP values were lower in female than male study participants at fasting (female: 4.1 ± 0.2 mg/dl; male: 5.4 ± 0.4 mg/dl; P < 0.004) as well as after 90 (female: 3.7 ± 0.2 mg/dl; male: 5.0 ± 0.2 mg/dl; P < 0.001) and 120 min (female: 3.8 ± 0.2 mg/dl; male: 5.0 ± 0.2 mg/dl; P < 0.001) of hyperinsulinemia. RBP was not different between pre- and postmenopausal women (data not shown). RBP did not correlate with EGP at any time of the clamp (basal: r = 0.15, P = 0.49; 90 min: r = −0.081, P = 0.7; 120 min: r = 0.3, P = 0.2).

RBP determined by quantitative Western blotting. Fasting plasma concentrations of RBP were comparable between IS (7.9 ± 0.5 mg/dl, n = 17) and IR (8.3 ± 0.6 mg/dl, n = 20; P = 0.63).

RBP determined by ELISA. Fasting plasma RBP concentrations were not different between IS (4.9 ± 0.3 mg/dl, n = 18) and IR (5.0 ± 0.4 mg/dl, n = 20; P = 0.84) study participants.

Results of nephelometry, ELISA, and quantitative Western blot were strongly associated with the highest correlation coefficients between nephelometry and quantitative Western blot (Table 2).

RBP determined by quantitative Western blotting. Fasting plasma concentrations of RBP were comparable between IS (7.9 ± 0.5 mg/dl, n = 17) and IR (8.3 ± 0.6 mg/dl, n = 20; P = 0.63).

RBP determined by ELISA. Fasting plasma RBP concentrations were not different between IS (4.9 ± 0.3 mg/dl, n = 18) and IR (5.0 ± 0.4 mg/dl, n = 20; P = 0.84) study participants.

Results of nephelometry, ELISA, and quantitative Western blot were strongly associated with the highest correlation coefficients between nephelometry and quantitative Western blot (Table 2).

PCI

Fasting plasma PCI active antigen was similar between both groups (IS: 107 ± 16% vs. IR: 95 ± 4%) (Fig. 3A).

| TABLE 2. Pearson's correlation of RBP concentrations obtained by nephelometry, ELISA, and quantitative Western blot |
|---------------------------------------------------|-------------------|-------------------|
| RBP nephelometry | RBP ELISA | RBP Western blot |
| RBP nephelometry | r = 0.623 | r = 0.736 |
| | P < 10⁻⁴ | P < 10⁻⁶ |
| RBP ELISA | r = 0.623 | r = 0.669 |
| | P < 10⁻⁴ | P < 10⁻⁵ |
| RBP Western blot | r = 0.736 | r = 0.669 |
| | P < 10⁻⁶ | P < 10⁻⁵ |
Correlation analyses

RBP. Plasma RBP did not significantly correlate with M (Fig. 3B) or OGTT 120/180 min (data not shown). When the relationship between RBP and M was determined separately for males and females, no difference was evident on the basis of gender (males: $r = 0.094, P = 0.77$; females: $r = -0.184, P = 0.36$). Also, fasting plasma RBP concentrations, determined by ELISA ($r = -0.27, P = 0.87$) and quantitative Western blotting ($r = -0.13, P = 0.44$) did not correlate with M.

RBP was positively correlated with body weight ($r = 0.407, P = 0.02$), height ($r = 0.415, P = 0.02$), body surface area ($r = 0.453, P = 0.007$), fat-free mass ($r = 0.494, P = 0.003$), triacylglycerides ($r = 0.592, P < 0.001$), and serum activity of aspartate aminotransaminase ($r = 0.581, P < 0.001$), alanine aminotransaminase ($r = 0.631, P < 0.001$), and $\gamma$GT ($r = 0.639, P < 0.001$). RBP was correlated positively with serum concentrations of creatinine ($r = 0.439, P = 0.009$) and uric acid ($r = 0.488, P = 0.003$) in females only and correlated negatively with low-density lipoprotein-cholesterol in males ($r = -0.591, P = 0.043$). No correlation with RBP was found for total cholesterol, HDL cholesterol, hemoglobin A1c, and FFAs as well as fat mass; thigh, waist, and hip circumference; waist to hip ratio; BMI; and age.

**Discussion**

We investigated the potential association of insulin-resistance and retinol-binding factors (RBP and PCI) in two groups of nondiabetic humans who were markedly different concerning insulin sensitivity but well matched for age, gender, and BMI. In this study, plasma RBP concentrations were measured with three independent methods including quantitative Western blotting, which is currently regarded as the gold standard in measuring RBP (25). We did not find any difference in plasma RBP levels between IR and IS humans. During elevated plasma insulin concentrations (OGTT and clamp test), plasma RBP was in part decreased when compared with respective basal values. Fasting PCI active antigen was not different between both groups. Both plasma RBP concentration and PCI active antigen were not related to insulin sensitivity.

**Study participants**

Our study population was healthy, middle aged, and moderately overweight. In IR, insulin resistance was certainly present in skeletal muscle, fat tissue, but, interestingly, not in liver, which suggests an early stage of insulin resistance. Previous reports from our laboratory indicate that hepatic insulin resistance seems to be related to chronic hyperglycemia, which was not found in any of our study participants (29, 30–32). In particular, these insulin-resistant humans appeared to be at high risk for developing the metabolic syndrome, whose definition and treatment are currently under debate (33). Thus, an early circulating marker of insulin resistance, as RBP is proposed to be (25), would certainly be helpful for patients’ identification and future treatment strategies.

**Plasma RBP**

Fasting plasma RBP concentrations measured by a highly sensitive nephelometric assay that has been certified and approved for clinical in vitro diagnostics were in the normal range (3–6 mg/dl according to the manufacturer) and were comparable with RBP concentrations measured by an recently developed ELISA (12). Furthermore, we verified our
results using quantitative Western blotting, which consistently showed approximately 2-fold higher RBP4 values than those measured by nephelometry when using a commercially available full-length recombinant standard for human RBP4. Interestingly, this difference was entirely dependent on the standard used in Western blotting because inclusion of and normalization to the nephelometric standard resulted in values that were highly comparable with nephelometric measurements. Of note, in contrast to recent observations, plasma RBP measured by three different methods including quantitative Western blotting was neither different between the groups nor associated with insulin resistance, measured by both clamp and OGTT. Differences in the study populations might have contributed to these divergent results. In these previous studies, elevated serum RBP concentrations were observed in insulin-resistant patients with obesity (8) and/or impaired glucose metabolism (12).

In contrast, in the present study, healthy nondiabetic, and only slightly overweight participants were included. Furthermore, insulin-sensitive and -resistant participants were well matched for gender, age, and BMI as well as fat and fat-free mass, with similar fasting insulin concentrations. Plasma concentrations of vitamin A and prealbumin were determined to exclude possible confounding effects on RBP concentration. Our results confirm the close association of vitamin A and prealbumin with RBP.

In our participants, plasma RBP levels were not related to insulin sensitivity but directly associated with anthropometric parameters such as body weight, height, fat-free mass, and body surface area and circulating molecules involved in liver, fat, and kidney metabolism such as serum creatinine, triglycerides, and transaminases/γGT.

From this it follows that plasma RBP in nondiabetic humans is not involved in insulin-mediated glucose disposal but rather depends on anthropometric properties and/or its release and elimination, the latter of which predominantly occurs in the kidney (34).

On the other hand, our data support a recent report from Janke et al. (13) that found no changes of serum RBP concentrations among lean, overweight, and obese women. Those women showed differences in insulin sensitivity, which was, however, measured by a mathematical model (homeostasis model assessment), which is correlated with but cannot substitute the hyperinsulimemic clamp (29).

Although circulating RBP levels were reported to be elevated in diabetic subjects (8) and RBP is produced from and stored in insulin-responsive tissues, the possible effect of hyperinsulinaemia on RBP was up to now only marginally investigated. Fasting plasma insulin was positively correlated to body weight and height as well as triglycerides, creatinine, uric acid, and liver enzymes, all of which are metabolites of organs that are responsible for the release and elimination of RBP. Furthermore, a short-term rise in plasma insulin does not appear to modulate circulating RBP concentrations. Thus, our findings do not support the hypothesis of insulin sensitivity modulation by proteins involved in retinol transport.

Acknowledgments

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