Limited Value of the Homeostasis Model Assessment to Predict Insulin Resistance in Older Men With Impaired Glucose Tolerance

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OBJECTIVE — Insulin resistance (IR) in older individuals is associated with risk factors for coronary artery disease. The glucose clamp measures IR directly, but the homeostasis model assessment (HOMA) of IR, referred to here as HOMA-IR, is based on fasting glucose and insulin and is less invasive and labor intensive. This method requires validation in the elderly.

RESEARCH DESIGN AND METHODS — We assessed the validity of HOMA-IR as an index of IR by comparing it to glucose infusion rates (GIRs) measured by a glucose clamp (600 pmol·min⁻¹·kg⁻¹) in 45 obese men (61 ± 8 years of age, mean ± SD) with normal glucose tolerance (NGT) (n = 21) or impaired glucose tolerance (IGT) (n = 24). We also evaluated relationships between body composition, exercise capacity, and IR.

RESULTS — Subjects with NGT had lower BMI (28 ± 3 vs. 31 ± 3 kg/m²), waist circumference (97 ± 9 vs. 105 ± 9 cm), waist-to-hip ratio (WHR) (0.93 ± 0.06 vs. 0.97 ± 0.05), and percent body fat (25 ± 6 vs. 30 ± 6) than subjects with IGT. Subjects with NGT also had lower areas above basal during the 2-h oral glucose tolerance test for glucose (274 ± 95 vs. 419 ± 124 mmol·min⁻¹) and insulin (38.142 ± 18.206 vs. 58.383 ± 34.408 pmol·min⁻¹) and lower HOMA-IR values (2.2 ± 0.8 vs. 4.2 ± 2.6) than subjects with IGT. GIR (µmol·kg⁻¹·FFM·min⁻¹) was higher in subjects with NGT than in subjects with IGT (53 ± 11 vs. 43 ± 14). HOMA-IR correlated with GIR in subjects with NGT (r = −0.59), but not in subjects with IGT (r = −0.13). GIR correlated with VO₂max in subjects with NGT (r = 0.58) and IGT (r = 0.42), but with WHR only in subjects with NGT (r = −0.53). HOMA-IR correlated with VO₂max (r = −0.57) and waist circumference (r = 0.54) in subjects with NGT, but with percent body fat in subjects with IGT (r = 0.54).

CONCLUSIONS — These findings indicate that HOMA-IR should not be used as an index of IR in older individuals who may be at risk for IGT, and suggest that lifestyle changes that increase VO₂max and decrease body fat may reduce IR in older people.


Aging is associated with obesity and physical inactivity, both of which increase the risk of insulin resistance (IR), coronary artery disease, and type 2 diabetes (1–3). The diagnosis of IR in older individuals is clinically relevant, because effective treatment through weight loss and regular exercise may reduce the risk of cardiovascular disease complications associated with the IR syndrome. Although the hyperinsulinemic-euglycemic clamp measures IR directly and is the “gold standard” (4), the homeostasis model assessment (HOMA) requires only fasting glucose and insulin concentrations (5,6). This mathematical model is based on the theory of a negative feedback loop between the liver and β-cells that regulates both fasting glucose and insulin concentrations and can be used to estimate pancreatic β-cell function and degree of IR. Therefore, it may be a useful noninvasive tool for clinicians to diagnose IR in older populations.

The HOMA for IR—referred to here simply as HOMA-IR—correlates highly and significantly with whole-body insulin action in nondiabetic and type 2 diabetic individuals (6,7). However, it appears that HOMA-IR does not adequately predict IR in all individuals. Indeed, several investigators report that HOMA-IR and insulin action do not correlate highly or significantly, particularly in individuals with impaired glucose tolerance (IGT) (8–10). These previous studies do not specifically examine the relationships between HOMA-IR and direct measures of insulin action using the euglycemic clamp in older individuals with IGT. This is particularly important, because 20% of individuals >50 years of age have IGT and 10% have type 2 diabetes (11). This study determines whether HOMA-IR is a good predictor of IR in middle-aged and older men with either normal glucose tolerance (NGT) or IGT. In addition, a secondary purpose of this study is to examine the relationships between indexes of IR, body composition, and exercise capacity.

RESEARCH DESIGN AND METHODS

Subjects — We recruited 45 healthy Caucasian nonsmoking sedentary obese (BMI >25 kg/m²) men (47–74 years of age) from the community for participation. Written informed consent was obtained from all individuals.
Homeostasis model assessment in older men

Table 1—Physical characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>NGT</th>
<th>IGT</th>
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<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.9 ± 8.5</td>
<td>60.9 ± 8.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.3 ± 13.1</td>
<td>91.5 ± 14.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 ± 2.6*</td>
<td>30.9 ± 2.8</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>25.2 ± 6.4*</td>
<td>30.0 ± 5.8</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>97.1 ± 9.5*</td>
<td>104.6 ± 9.2</td>
</tr>
<tr>
<td>WHR</td>
<td>0.93 ± 0.06*</td>
<td>0.97 ± 0.05</td>
</tr>
<tr>
<td>VO₂max (ml · kg⁻¹ · min⁻¹)</td>
<td>31.2 ± 7.2</td>
<td>28.5 ± 6.4</td>
</tr>
</tbody>
</table>

Data are means ± SD unless otherwise stated. *Significantly different from IGT, P < 0.05.

according to the guidelines of the institutional review boards for human studies at Bayview Johns Hopkins and the School of Medicine at the University of Maryland at Baltimore. All subjects underwent a thorough medical screening, including a history and physical examination, fasting blood profile, and a graded exercise treadmill test before entering the study. All of the clamp data have been previously reported in other publications (12–14).

Body composition
BMI was calculated by dividing the weight of the subject by the height squared (kilograms divided by meters squared). Body density was determined by hydrostatic weighing, and percent body fat was calculated (15) after correction for residual lung volume. Fat-free mass (FFM) was calculated as body mass minus fat mass. The waist-to-hip ratio (WHR), an index of the pattern of regional body fat distribution, was calculated by dividing the waist measurement (minimum circumference of the abdomen) by the circumference of the buttocks at the maximal gluteal protuberance (hip measurement).

Measurement of VO₂max
A treadmill VO₂max test was performed on each subject on at least 2 separate days, as previously described (12). A true VO₂max was considered to be attained if two of the following three criteria were met: 1) respiratory exchange ratio at maximal exercise >1.10, 2) maximal heart rate >90% of age-predicted maximum (220 – age), and 3) a plateau in VO₂ (<200 ml/min change in the VO₂) during the last stages of exercise. Usually, a true VO₂max was attained on the second test, but if the results for the two exercise tests differed by >200 ml/min, an additional VO₂max test was performed to meet these criteria.

Metabolic testing
For 3 days before each metabolic test and during testing, subjects were provided with an American Heart Association weight-maintaining phase 1 diet (16). If body weight varied by >0.25 kg during periods of testing, research tests were delayed for 48 h, and subjects were provided with additional days of food until weight stability was achieved. All metabolic tests were performed in the morning after a 12-h overnight fast.

Oral glucose tolerance test
Blood samples were drawn for the measurement of plasma glucose and insulin before and at 30-min intervals for 2 h after the ingestion of 40 g glucose/m² body surface area (17). The areas under the curves for the glucose and insulin responses during the 2-h oral glucose tolerance test (OGTT) were calculated above the basal level using a trapezoidal model.

Hyperinsulinemic-euglycemic glucose clamp
Whole-body insulin action was measured using the one-step hyperinsulinemic-euglycemic glucose clamp technique (4). Briefly, an intravenous catheter was inserted into an antecubital vein for infusion of insulin and glucose, and a second catheter was inserted into a dorsal hand vein for blood sampling. The hand was then placed in a warming box thermostatically controlled at 70°C to arterioalize the blood and allowed to equilibrate for 30 min before baseline samples for glucose and insulin were obtained. After a priming dose of insulin, Humulin insulin (Eli Lilly, Indianapolis, IN) was infused at a constant rate of 600 pmol · m⁻² · min⁻¹. Plasma glucose levels were measured at 5-min intervals using the glucose oxidase method (Beckman Instruments, Fullerton, CA) and maintained at basal levels with a variable infusion of 20% glucose, which was adjusted according to a computerized algorithm. Samples were obtained at 10-min intervals during the clamp for subsequent measurement of plasma insulin levels by radioimmunoassay (18).

Calculations
Mean glucose infusion rates (GIRs), normalized for FFM (µmol · kg⁻¹ · FFM · min⁻¹), were calculated at 10-min intervals and averaged over the last 30 min of the clamp. Steady-state plasma insulin levels were averaged over the same interval. HOMA-IR was calculated as previously described (19): [(fasting insulin (µU/ml) × fasting glucose [mmol/l])/22.5].

Statistical analyses
Data were analyzed using standard statistical software packages (20). Plasma insulin concentrations and HOMA-IR values were log-transformed to yield a normal distribution before analyses. Differences between groups were determined by t tests. Pearson correlation coefficients were calculated between selected variables and GIR and HOMA-IR. When multiple independent variables correlated with GIR and HOMA-IR, variables with statistically significant correlations were entered into stepwise multiple regression analysis to determine the best predictors of GIR and HOMA-IR. P values <0.05 were considered statistically significant. All data are presented as the means ± SD.

RESULTS

Subject characteristics
The 45 subjects were grouped according to glucose tolerance status, as determined by the OGTT (21). There were no differences in age, body weight, or VO₂max between the 21 men with NGT compared with the 24 men with IGT (Table 1). The group with NGT had significantly lower percent body fat, waist circumference, WHR, and BMI in comparison with the group with IGT (Table 1).

Metabolic differences also were observed between the two groups. The NGT group had significantly lower fasting glucose and insulin concentrations and 2-h OGTT glucose and insulin areas (above basal) in comparison with the IGT group (Table 2). During the hyperinsulinemic-euglycemic clamp, the NGT group had a significantly higher GIR than the IGT group, despite no difference in the insulin concentrations during the 600 pmol · m⁻² · min⁻¹ insulin infusion (Table 2). HOMA-IR was signifi-
cantly lower in the NGT group than in the IGT group (Table 2).

**Relationships among indexes of IR, subject characteristics, and glucose tolerance**

There was a significant relationship between HOMA-IR and GIR when both groups were combined ($r = -0.39$, $P < 0.05$; Fig. 1). However, when the analysis was performed separately on each group, HOMA-IR and GIR correlated highly and significantly in the NGT group ($r = -0.59$, $P < 0.01$; Fig. 1) but not in the IGT group ($r = -0.13$, NS), indicating that the significant correlation in the entire group was due to the NGT group. One subject in the NGT group had a high GIR (72.7 µmol kg$^{-1}$ FFMin$^{-1}$) and a low HOMA-IR (0.64, log value $-0.19$), indicating high sensitivity to insulin. In Fig. 1, this subject appears as an outlier, with a negative value for the log transformation of HOMA-IR ($-0.19$).

When this subject is removed from the analysis, the relationship between HOMA-IR and GIR for the entire population ($r = -0.31$, $P < 0.05$) and the NGT group alone ($r = -0.46$, $P < 0.05$) remains significant.

The relationship between GIR and $V_{O2max}$ was statistically significant in both the NGT and IGT groups, whereas the correlation between GIR and WHR was significant in the NGT group only (Table 3). There was no significant relationship between GIR and percent body fat, BMI, or waist circumference in either group. In a stepwise multiple regression with both groups combined, only $V_{O2max}$ predicted GIR ($r^2 = 0.14$, $P < 0.05$).

There were significant correlations between HOMA-IR and waist circumference and $V_{O2max}$ only in the NGT group (Table 3). The relationship between HOMA-IR and percent body fat was significant in the IGT group and approached statistical significance in the NGT group (Table 3, $P = 0.09$). There was no significant relationship between HOMA-IR and BMI or WHR in either group. In a stepwise multiple regression with both groups combined, HOMA-IR was predicted only by percent body fat ($r^2 = 0.25$, $P < 0.05$). For the NGT group only, both $V_{O2max}$ ($r^2 = 0.29$, $P < 0.05$) and waist circumference ($r^2 = 0.12$, $P < 0.05$) predicted HOMA-IR ($r^2_{total} = 0.41$, $P < 0.05$).

The relationship between 2-h OGTT insulin areas and GIR was statistically significant for both the NGT and IGT groups. The relationship between the 2-h OGTT insulin area and HOMA-IR was statistically significant in the IGT group only and approached statistical significance in the NGT group ($P = 0.06$). In a stepwise multiple regression, the 2-h OGTT insulin area was predicted by both HOMA-IR ($r^2 = 0.32$, $P < 0.05$) and GIR ($r^2 = 0.09$, $P < 0.05$).

<table>
<thead>
<tr>
<th>Fasting insulin (pmol/l)</th>
<th>NGT</th>
<th>IGT</th>
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<tbody>
<tr>
<td>58.5 ± 4.5*</td>
<td>94.8 ± 10.9</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.1 ± 0.3*</td>
<td>5.8 ± 0.6</td>
</tr>
<tr>
<td>2-h OGTT insulin area (pmol · min⁻¹)</td>
<td>38.142 ± 18.206*</td>
<td>58.383 ± 34.408</td>
</tr>
<tr>
<td>2-h OGTT glucose area (mmol · min⁻¹)</td>
<td>274 ± 9.5*</td>
<td>419 ± 12.4</td>
</tr>
<tr>
<td>GIR (µmol · kg⁻¹ FFM · min⁻¹)</td>
<td>52.5 ± 10.8*</td>
<td>43.4 ± 13.7</td>
</tr>
<tr>
<td>Insulin during clamp (pmol/l)</td>
<td>1,835 ± 83</td>
<td>1,999 ± 104</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.2 ± 0.8*</td>
<td>4.2 ± 2.6</td>
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</tbody>
</table>

Data are means ± SD. *Significantly different from IGT, $P < 0.05$. |

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**CONCLUSIONS** — The results of this study show that HOMA-IR is a statistically significant predictor of IR in middle-aged and older men with NGT, but not in men with IGT. Although the HOMA-IR model is a relatively noninvasive and convenient way to estimate IR, its use and validity in older individuals may be limited, since the prevalence of IGT increases with age. In contrast, the insulin response during an OGTT correlated with IR measured during the glucose clamp as well as with HOMA-IR in subjects with either NGT or IGT. These findings indicate that HOMA-IR should not be used as an index of IR in older obese individuals or in individuals at high risk for IGT. Rather, the insulin response during an OGTT may be a better index of IR in older subjects when glucose clamps cannot be performed to directly assess insulin action.

The absence of a relationship between HOMA-IR and GIR in individuals with IGT in this study supports the findings of Anderson et al. (8), but differs from those of Matsuda and DeFronzo (7). Since both studies involved subjects with an average age of 40 years, the findings are not applicable to the elderly. The lack of a correlation in subjects with IGT in our study may be because the relationship between HOMA-IR and GIR is not linear, particularly at the upper limits of HOMA-IR values, which may be more common in older individuals with IGT. Inaccurate assumptions that may limit the ability of HOMA-IR to accurately

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Figures and tables are not included in this text. For the complete article, please refer to the source.
predict IR were recently reviewed (22). These include the fact that HOMA-IR is based on fasting glucose and insulin concentrations, both of which are measures that reflect insulin sensitivity in the basal state. Thus, it may not provide a good measure of insulin action in insulin-sensitive tissues, such as muscle, in the postprandial phase. Furthermore, the fasting state does not accurately represent both the hepatic and peripheral components of insulin action, thus limiting its ability to assess IR. In addition, one of the assumptions of the HOMA is that the fasting glucose and insulin concentrations reflect the normal insulin secretory response after a glucose challenge. This may not necessarily be true in all individuals, particularly those with IGT. Furthermore, HOMA assumes that fasting insulin is directly related to whole-body IR. Since few studies have examined insulin action at low insulin concentrations, it would be difficult to extrapolate values under basal conditions from the results of a glucose clamp normally performed at physiological insulin levels. IR is primarily manifest in the postprandial state, when the majority of glucose uptake occurs in insulin-independent tissues.

Table 3—Correlations between GIR, HOMA-IR, and subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>HOMA-IR NGT</th>
<th>IGT</th>
<th>GIR NGT</th>
<th>IGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂max (ml·kg⁻¹·min⁻¹)</td>
<td>-0.57*</td>
<td>-0.37</td>
<td>0.58*</td>
<td>0.42†</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.54†</td>
<td>0.13</td>
<td>-0.36</td>
<td>0.02</td>
</tr>
<tr>
<td>WHR</td>
<td>0.26</td>
<td>0.01</td>
<td>-0.53†</td>
<td>-0.02</td>
</tr>
<tr>
<td>BMI</td>
<td>0.28</td>
<td>0.07</td>
<td>0.15</td>
<td>-0.12</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>0.36</td>
<td>0.54†</td>
<td>-0.17</td>
<td>-0.17</td>
</tr>
<tr>
<td>2-h OGTT insulin area</td>
<td>0.42</td>
<td>0.54*</td>
<td>-0.46†</td>
<td>-0.44†</td>
</tr>
</tbody>
</table>

*Statistically significant, P < 0.01; †statistically significant, P < 0.05.

In the present study, there was a significant correlation between HOMA-IR and both waist circumference and VO₂max in individuals with NGT and between HOMA-IR and percent body fat in individuals with IGT. Since these studies were in middle-aged and older men, obesity and WHR may be related, because older men tend to deposit excess fat centrally. This supports the tenet that low VO₂max and central obesity are associated with IR in older individuals and suggests that treatment modalities that increase VO₂max and decrease body fat may reduce the risk for the development of IR in healthy older men. This notion is supported by our recent findings that high-intensity aerobic exercise and weight loss increase insulin action, thus increasing insulin sensitivity in obese hypertensive men with the metabolic abnormalities associated with the IR syndrome (14). In addition, other studies have observed improved insulin sensitivity in older individuals after a regular aerobic exercise program (26,27).

The present study may be one of the first to examine the relationships between insulin action measured by the glucose clamp and HOMA-IR with measures of body composition and exercise capacity in middle-aged and older individuals, it included only Caucasian men, none of whom had type 2 diabetes. Thus, the findings may apply only to nondiabetic obese older Caucasian men, not older women, older individuals with type 2 diabetes, or older men from other ethnic groups. Furthermore, our findings show that VO₂max and percent body fat are the best independent predictors of GIR and HOMA-IR. This result suggests that lifestyle changes that increase VO₂max and decrease central obesity may prevent IR and reduce the risk for type 2 diabetes and the cardiovascular disease complications associated with the IR syndrome in older men.

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References

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