Impact of Differences in Fasting Glucose and Glucose Tolerance on the Hyperbolic Relationship Between Insulin Sensitivity and Insulin Responses

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OBJECTIVE — To determine whether the hyperbolic relationship between insulin sensitivity and the acute insulin response to glucose (AIRg) exists in subjects with impaired fasting glucose (IFG) or decreased glucose tolerance.

RESEARCH DESIGN AND METHODS — We studied 219 healthy subjects (88 male and 131 female subjects, aged 26–75 years) with fasting plasma glucose (FPG) <6.1 mmol/l. Subjects underwent an intravenous glucose tolerance test to determine the insulin sensitivity index (SI), AIRg, and the glucose disappearance constant (Kg), the latter a measure of intravenous glucose tolerance.

RESULTS — SI and AIRg were inversely related for the entire cohort, and this relationship was not significantly different from hyperbolic. The inverse relationship between SI and AIRg was not significantly different when compared between groups based on fasting glucose (normal fasting glucose [NFG], FPG <5.56 mmol/l vs. IFG, FPG 5.56–6.11 mmol/l) or by the Kg quartile. However, the curve relating SI and AIRg was left shifted in the IFG compared with NFG group (P < 0.001) and was progressively more left shifted with decreasing Kg (P < 0.001), consistent with decreasing β-cell function. These changes were not observed for the curves relating SI and fasting insulin, suggesting that in the fasting state β-cell function is maintained even in patients with mild IFG. Finally, the disposition index (DI) (SI × AIRg) was calculated as a measure of β-cell function. The DI progressively decreased with increasing FPG, even in the group of subjects classified as NFG.

CONCLUSIONS — The inverse relationship between insulin sensitivity and AIRg is consistent with a hyperbola not only in subjects with normal glucose tolerance but also with mild IFG or decreased Kg. Based on a hyperbolic relationship, a decrease in β-cell function can be detected as FPG increases, even in patients who are normal glucose tolerant.


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Abbreviations: AIRg, acute insulin response to glucose; DI, disposition index; FPG, fasting plasma glucose; IFG, impaired fasting glucose; NFG, normal fasting glucose.

A table elsewhere in this issue shows conventional and SI units and conversion factors for many substances.

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had previously participated in a study of the effects of insulin sensitivity on the plasma lipid profile after egg consumption (11). Subjects were otherwise healthy with no history of diabetes, dyslipidemia, uncontrolled hypertension, or vascular disease and no evidence of renal or hepatic dysfunction, uncontrolled thyroid disease, or anemia. One subject was excluded as an outlier since his fasting insulin was 3.24 SDs away from the regression line and was highly influential: exclusion of this subject did not affect the statistical conclusions. A second subject’s AIRg value was highly influential with a statistical conclusions. A second subject’s exclusion of this subject did not affect the excluded as an outlier since his fasting thyroid disease, or anemia. One subject was vascular disease and no evidence of renal lipidemia, uncontrolled hypertension, or subjected to the University of Washington.

Frequently sampled intravenous glucose tolerance test A tolbutamide-modified frequently sampled intravenous glucose tolerance test was performed as previously described (11) to quantify insulin sensitivity, AIRg, and intravenous glucose tolerance.

Assays Plasma glucose was measured using the glucose oxidase method. Plasma immunoreactive insulin levels were measured using a modification of a double-antibody radioimmunoassay (12).

Calculations FPG and insulin values were calculated as the average of the three basal samples. The insulin sensitivity index (S\text{\textsubscript{i}}) was calculated using Bergman’s minimal model of glucose kinetics (13). AIRg was calculated as the mean incremental insulin response above basal between 2 and 10 min after the intravenous glucose bolus. The glucose disappearance constant (K\text{\textsubscript{g}}) was calculated as the slope of the natural log of glucose from 10 to 19 min, expressed as percent change per minute. \beta-Cell function was determined as the DI, which was calculated as the product of S\text{\textsubscript{i}} and AIRg.

Data analysis and statistical approach To determine whether the relationship between the dependent (fasting insulin or AIRg) and independent (S\text{\textsubscript{i}}) variable was hyperbolic (x \times y = constant), we estimated the natural logarithm (ln) of fasting insulin or AIRg as a linear function of ln(S\text{\textsubscript{i}}) using regression. If the hyperbolic relationship exists, the slope of the regression line would be -1 (5). The regression method we used corrects for the underestimation of slope when measurement error is present in both the x and y variable (14, 15). Briefly, when error is present in both x and y variables, the slope that is determined by ordinary least squares regression is underestimated since ordinary least squares assumes that all error is present in the y variable. The regression method we used corrects this bias by incorporation of a factor that is the ratio of the variances of the error in the y to x variables. These error estimates for measurement of S\text{\textsubscript{i}}, AIRg, and fasting insulin were based on the day-to-day coefficients of variation for these measures in our laboratory (16.9\% for S\text{\textsubscript{i}}, 20.6\% for AIRg, and 10.2\% for fasting insulin (16)). A hyperbolic relationship was presumed if the ± 2 SD confidence limit of the slope included -1.00.

Slopes are expressed as the means ± SD calculated using the bootstrap method (17). Briefly, this method estimates the statistical characteristics of a population by taking repeated samples of a population sample with replacement. For the current analysis, to determine the SD of the slope, 10,000 sets of data were randomly selected (with replacement) from the original data. The slope for each set was computed, from which the SD of these 10,000 slopes was then computed. The y-intercept was also computed from the adjusted slope value, and the y-intercept SD was computed in a similar manner.

Subjects were subdivided for analysis using three different methods: 1) by fasting glucose into normal fasting glucose (NFG) (FPG < 5.6 mmol/l) and impaired fasting glucose (IFG) (FPG 5.6–6.1 mmol/l), 2) by quartiles of FPG, and 3) by quartiles of K\text{\textsubscript{g}}.

The slopes and intercepts of the estimated regression lines when subdivided by NFG versus IFG were compared with each other using t tests on the adjusted slope and y-intercept values. For comparison of the K\text{\textsubscript{g}} quartiles, ANOVA was performed. Since standard ANOVA does not incorporate the error in the independent variables, we also confirmed the ANOVA results by performing individual t tests on the corrected slopes and y-intercepts with Bonferroni correction (results not shown), which yielded similar results. As the slopes were not statistically different between the groups, a common slope was used for all groups when examining differences in the y-intercepts. Residual plots for all regressions were examined and showed no evidence of heteroscedasticity, nonnormality, or lack of fit.

Comparison between groups was performed by either an independent sample t test or by ANOVA with Bonferroni post hoc analysis. Correlations were computed using linear regression. Data that were not normally distributed were log transformed to achieve normal distribution. Data are presented as means ± SE, unless otherwise specified. A two-sided P \textless 0.05 was considered significant.

RESULTS

Subject characteristics

The study cohort comprised 219 subjects with a broad range of age (26–75 years) and BMI (18.7–40.4 kg/m\textsuperscript{2}). Further, they had broad ranges of fasting insulin (18–276 pmol/l), S\text{\textsubscript{i}} (0.7–25.3 \times 10\textsuperscript{-5} min\textsuperscript{-1}/pmol/l), AIRg (32–2638 pmol/l), DI (245–6461 \times 10\textsuperscript{-5} min\textsuperscript{-1}), and K\text{\textsubscript{g}} (0.6–3.9\%/min).

Hyperbolic relationships between insulin sensitivity and fasting insulin and insulin sensitivity and AIRg in the entire cohort

For the entire cohort, there was a significant correlation between ln(S\text{\textsubscript{i}}) and ln(fasting insulin) (r = -0.72, P < 0.001) and between ln(S\text{\textsubscript{i}}) and ln(AIRg) (r = -0.37, P < 0.001). The slopes for these relationships were not significantly different from -1 (ln(S\text{\textsubscript{i}}) vs. ln(fasting insulin) slope = -0.96 ± 0.07; ln(S\text{\textsubscript{i}}) vs. ln(AIRg) slope = -0.75 ± 0.14), consistent with a hyperbolic relationship between the two variables.

Effect of fasting glucose on the hyperbolic relationships, insulin sensitivity, and \beta-cell function

BMI and fasting insulin were higher and S\text{\textsubscript{i}}, AIRg, the DI, and K\text{\textsubscript{g}} were lower in the IFG category (Table 1). The slope for the relationship between ln(S\text{\textsubscript{i}}) and ln(fasting insulin) was -0.99 ± 0.09 for NFG and -1.01 ± 0.13 for IFG. When NFG and IFG were compared, neither the slopes nor the intercepts for the relationship between ln(S\text{\textsubscript{i}}) and ln(fasting insulin) differed. Thus, when the hyperbolic relationships between these two variables were plotted, the curves for both categories were superimposable (Fig. 1A).
Table 1—Characteristics of the subjects subdivided by NFG and IFG, quartile of fasting plasma glucose, and $K_g$ quartiles

<table>
<thead>
<tr>
<th>Fasting glucose range (mmol/l)</th>
<th>NFG</th>
<th>IFG</th>
<th>FPG Q1</th>
<th>FPG Q2</th>
<th>FPG Q3</th>
<th>FPG Q4</th>
<th>P values by ANOVA for glucose quartiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>156</td>
<td>63</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.7 ± 0.8</td>
<td>53.3 ± 1.3</td>
<td>49.7 ± 1.2</td>
<td>52.3 ± 1.5</td>
<td>54.5 ± 1.5</td>
<td>52.3 ± 1.3</td>
<td>&lt;0.001, 1 vs. 4; &lt; 0.05, 2 vs. 4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 0.3</td>
<td>28.0 ± 0.5*</td>
<td>24.6 ± 0.5</td>
<td>26.0 ± 0.6</td>
<td>26.3 ± 0.5</td>
<td>28.0 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.2 ± 0.02</td>
<td>5.8 ± 0.02*</td>
<td>4.86 ± 0.02</td>
<td>5.21 ± 0.01</td>
<td>5.46 ± 0.01</td>
<td>5.83 ± 0.01</td>
<td>&lt;0.001 for each</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>56.1 ± 2.7</td>
<td>70.9 ± 4.7†</td>
<td>45.2 ± 2.8</td>
<td>61.0 ± 5.6</td>
<td>65.5 ± 5.0</td>
<td>70.1 ± 4.8</td>
<td>≤0.001, 1 vs. 4; &lt;0.05, 1 vs. 3</td>
</tr>
<tr>
<td>$S_1$ ($\times 10^{-3}$ min$^{-1}$/pmol/l)</td>
<td>7.19 ± 0.33</td>
<td>4.79 ± 0.30*</td>
<td>9.04 ± 0.69</td>
<td>6.37 ± 0.40</td>
<td>5.76 ± 0.43</td>
<td>4.79 ± 0.33</td>
<td>≤0.001, 1 vs. 2, 3, and 4</td>
</tr>
<tr>
<td>AIRg (pmol/l)</td>
<td>356 ± 16</td>
<td>300 ± 44*</td>
<td>341 ± 25</td>
<td>363 ± 29</td>
<td>346 ± 25</td>
<td>311 ± 50</td>
<td>NS</td>
</tr>
<tr>
<td>DI ($\times 10^{-3}$ min$^{-1}$)</td>
<td>2,215 ± 104</td>
<td>1,132 ± 93*</td>
<td>2,623 ± 186</td>
<td>2,028 ± 168</td>
<td>1,798 ± 160</td>
<td>1,151 ± 98</td>
<td>≤0.001, 1 vs. 3 and 4 and 2 vs. 4; &lt; 0.05, 1 vs. 2 and 3 vs. 4</td>
</tr>
<tr>
<td>$K_g$ (%/min)</td>
<td>1.83 ± 0.05</td>
<td>1.37 ± 0.04*</td>
<td>1.98 ± 0.01</td>
<td>1.76 ± 0.08</td>
<td>1.66 ± 0.06</td>
<td>1.38 ± 0.05</td>
<td>&lt;0.001, 1 and 2 vs. 4; &lt; 0.05 1 vs. 3 and 3 vs. 4</td>
</tr>
</tbody>
</table>

$K_g$ range (%/min) | $K_g$ Q1 | $K_g$ Q2 | $K_g$ Q3 | $K_g$ Q4 |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>(n)</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>Age (years)</td>
<td>—</td>
<td>—</td>
<td>54.3 ± 1.3</td>
<td>53.9 ± 1.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>—</td>
<td>—</td>
<td>26.9 ± 0.6</td>
<td>26.5 ± 0.6</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>—</td>
<td>—</td>
<td>5.55 ± 0.05</td>
<td>5.44 ± 0.04</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>—</td>
<td>—</td>
<td>61.8 ± 5.9</td>
<td>64.1 ± 5.0</td>
</tr>
<tr>
<td>$S_1$ ($\times 10^{-3}$ min$^{-1}$/pmol/l)</td>
<td>—</td>
<td>—</td>
<td>5.87 ± 0.54</td>
<td>5.51 ± 0.43</td>
</tr>
<tr>
<td>AIRg (pmol/l)</td>
<td>—</td>
<td>—</td>
<td>207 ± 16</td>
<td>274 ± 19</td>
</tr>
<tr>
<td>DI ($\times 10^{-3}$ min$^{-1}$)</td>
<td>—</td>
<td>—</td>
<td>999 ± 81</td>
<td>1,252 ± 72</td>
</tr>
<tr>
<td>$K_g$ (%/min)</td>
<td>—</td>
<td>—</td>
<td>1.11 ± 0.02</td>
<td>1.47 ± 0.01</td>
</tr>
</tbody>
</table>

Data are means ± SE. *P ≤ 0.001 vs. NFG by t test; †P = 0.005.
The slope for the relationship between \( \ln(S_i) \) and \( \ln(AIR_g) \) for NFG was \(-0.71 \pm 0.11\) and that for IFG was \(-1.30 \pm 0.34\). Although the slope for NFG did not include \(-1\), the slope for the entire cohort included \(-1\), and when the slopes of the two groups were compared they were not significantly different from each other (\( P = 0.10\)). However, the \( y \)-intercept was significantly lower in IFG compared with NFG (\( P < 0.0001\)). Thus, when the hyperbolic curves were plotted, the curve relating \( S_i \) and \( AIR_g \) was leftward and downward shifted in the IFG group consistent with a decrease in \( \beta \)-cell function (Fig. 1B). This finding is in keeping with the lower DI in IFG (Table 1).

When the cohort was divided into quartiles by FPG, \( S_i \) decreased significantly from quartile 1 to 2 with much smaller and nonsignificant decrements in insulin sensitivity observed between quartiles 2, 3, and 4, suggesting an early decrease in insulin sensitivity (Table 1). \( AIR_g \) failed to increase appropriately in response to this decrease in \( S_i \), resulting in a progressive decrease in the DI (Table 1). These findings were confirmed by linear regression with both \( S_i \) [\( \ln(S_i) \) vs. FPG: \( r = -0.36, P < 0.001\)] and the DI [\( \ln(DI) \) vs. FPG: \( r = -0.51, P < 0.001\)] decreasing with increasing FPG, while there was only a weak negative correlation between \( AIR_g \) and FPG [\( \ln(AIR_g) \) vs. FPG: \( r = -0.19, P < 0.01\)]. As illustrated in Fig. 2, there did not appear to be a glucose threshold above which \( S_i \), \( AIR_g \), and the DI declined. In fact, the greatest decrease in \( S_i \) occurred between quartiles 1 and 2, where all subjects had fasting glucose in the normal range.

The slopes for the relationship between \( \ln(S_i) \) and \( \ln(AIR_g) \) for each of the \( K_g \) quartiles were Q1: \(-0.99 \pm 0.12\), Q2: \(-0.92 \pm 0.10\), Q3: \(-1.17 \pm 0.23\), and Q4: \(-1.03 \pm 0.18\). There was no difference in slope for the relationship between \( \ln(S_i) \) and \( \ln(AIR_g) \) in the highest \( K_g \) quartile versus the other three groups (\( P = 0.02\)). Thus, when the hyperbolic relationships between these two variables were plotted, the curves for each quartile were superimposed except for the highest \( K_g \) quartile, which was slightly higher and shifted to the right (Fig. 1C).

The slopes for the relationship between \( \ln(S_i) \) and \( \ln(AIR_g) \) for each \( K_g \) quartile were Q1: \(-0.79 \pm 0.18\), Q2: \(-0.61 \pm 0.07\), Q3: \(-0.92 \pm 0.20\), and Q4: \(-0.72 \pm 0.10\). There was no significant difference in slopes (\( P = 0.73\)), but there were significant differences among the intercepts (\( P < 0.0001\)), with intercept values decreasing with decreasing \( K_g \) quartile. Thus, the curve relating \( S_i \) and \( AIR_g \) shifted progressively leftward and downward with decreasing \( K_g \), consistent with decreasing \( \beta \)-cell function (Fig. 1D). In keeping with this shift in the hyperbolic curves, the DI decreased progressively with decreasing \( K_g \) (\( r = 0.744, P < 0.001\)).

**CONCLUSIONS** — While a hyperbolic relationship between insulin sensitivity and insulin responses has previously been shown in a young healthy population (5), the present study extends this previous analysis by demonstrating that a similar inverse relationship exists between insulin sensitivity and insulin responses in subjects with abnormal glucose metabolism. We found no significant difference in the slopes for the relationship between \( \ln(S_i) \) and \( \ln(fasting \ insulin) \) and between \( \ln(S_i) \) and \( \ln(AIR_g) \) between subjects with NFG and those with mild IFG (FPG between 5.6 and 6.1 mmol/l;
100 and 110 mg/dl) and between subjects when divided into quartiles by intravenous glucose tolerance (Kg). These findings support the hypothesis that the relationship between insulin sensitivity and AIRg is similar in subjects with normal and abnormal glucose metabolism.

Based on a hyperbolic relationship, use of the DI (when considering Si and AIRg) as a measure of \( \beta \)-cell function can provide a means to assess physiology and pathophysiology in population groups within these ranges of fasting glucose and glucose tolerance. Using this approach, we demonstrate a progressive impairment in \( \beta \)-cell function with increasing fasting glucose, even in subjects considered to be normal.

The concept of interpreting insulin responses in light of the prevailing level of insulin sensitivity is an important one. If this is not done, erroneous conclusions may be drawn. For example, an obese insulin-resistant subject with IGT may have a higher AIRg than a lean insulin-sensitive subject. However, based on the inverse relationship between insulin sensitivity and AIRg, calculation of the DI demonstrates that the greater insulin response in the obese insulin-resistant subject is not adequate to fully compensate for the lower insulin sensitivity. Thus, evaluation of \( \beta \)-cell function in subjects with normal and abnormal glucose metabolism requires knowledge of the prevailing insulin sensitivity.

In addition to determining the effect of differences in fasting glucose status on the hyperbolic relationship, we assessed the relationship between increased fasting glucose as a continuous variable and measures of insulin sensitivity and \( \beta \)-cell function. With increasing fasting glucose, Si decreases progressively but AIRg fails to increase appropriately. Thus, a progressive decrease in the DI occurs. This finding is of interest, as it suggests that there is no definite threshold of fasting glucose at which reductions in \( \beta \)-cell function occur. This is in contrast to the findings of Godsland et al. (18) who observed that AIRg declined above a fasting glucose between 4.97 and 5.42 mmol/l. In keeping with the results of our study, others using both intravenous (19,20) and oral glucose tolerance test methods (21) found decreases in insulin responses adjusted for insulin sensitivity in subjects with higher fasting glucose levels that were still well within the normal range. These findings taken together suggest the possibility that even in subjects with normal fasting glucose levels, higher fasting glucose levels are associated with decreased insulin sensitivity and an inadequate compensatory insulin response. Thus, the underlying physiology that eventually leads to IGT and type 2 diabetes may be manifest much earlier than defined by the current clinical criteria for IFG.

It should be recognized that this approach using the DI to provide a measure of \( \beta \)-cell function will not be useful in groups of subjects lacking a first-phase insulin response. It is well recognized that AIRg is typically absent in individuals with type 2 diabetes (22,23), and it has been shown that this response is lacking when fasting glucose exceeds 6.4 mmol/l (115 mg/dl) (23). Given the selection criteria for our cohort, which excluded subjects with diabetes and subjects with a fasting glucose >6.1 mmol/l, we cannot be certain that the hyperbolic relationship between Si and AIRg exists at higher glucose levels or in subjects with diabetes. However, we believe it would be unlikely given the lack of an AIRg in subjects with fasting glucose >6.4 mmol/l. The hyperbolic relationship has also been shown to
exist for certain other measures of insulin release, including the glucose potentiation slope and the maximal insulin secretory response to arginine (AIRmax) (5). While we did not assess these parameters in this study, glucose potentiation is still present in subjects with diabetes (24,25). Therefore, the hyperbolic relationship between S1 and AIRmax probably still exists in these subjects and thus could provide a measure of β-cell function in these groups.

In the current study, the overall slope of ln(S1) versus ln(AIRmax) was not different from −1.0, indicating that the relationship was not significantly different from a hyperbola. Other investigators have provided study results that indicate that this relationship is not hyperbolic (26). However, as with any mathematical model, deviations from the model may reflect either analytical problems or complexities in the underlying physiology that are not fully accounted for by the model. One of the analytical problems that other investigators (26) have not considered is the fact that there is measurement error in both variables. When there is measurement error in both the dependent (y) and predictor (x) variables, the use of ordinary least squares that assumes measurement error in only the dependent variable results in the slope of the regression line being underestimated. For example, using the present data, the unadjusted slope for ln (insulin sensitivity) versus ln(fasting insulin) was −0.61 without correction and −0.96 with correction. Additionally, when the data are inherently noisy and a substantial portion of the error is in the independent variable, small changes in the error estimates can have dramatic effects on the slope.

In summary, we have demonstrated that the inverse relationships between S1 and both fasting insulin and AIRmax are not significantly different from a hyperbola in subjects with mild IFG and those with reduced glucose tolerance. Based on these findings, the product of AIRmax and insulin sensitivity, which is known as the DI, provides a good measure of β-cell function and is applicable in patients with normal glucose tolerance or mild IFG. Thus, use of the DI may help to identify individuals at increased risk of developing diabetes and to assess the impact of interventions that are anticipated to change glucose tolerance.

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