

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 (AIR_g) 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) <6.11 mmol/L. Subjects underwent an intravenous glucose tolerance test to determine the insulin sensitivity index (S_i), AIR_g, and the glucose disappearance constant (K_g), the latter a measure of intravenous glucose tolerance.

RESULTS — S_i and AIR_g were inversely related for the entire cohort, and this relationship was not significantly different from hyperbolic. The inverse relationship between S_i and AIR_g 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 K_g quartile. However, the curve relating S_i and AIR_g was left shifted in the IFG compared with NFG group ($P < 0.001$) and was progressively more left shifted with decreasing K_g ($P < 0.001$), consistent with decreasing β -cell function. These changes were not observed for the curves relating S_i 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) (S_i × AIR_g) 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 AIR_g is consistent with a hyperbola not only in subjects with normal glucose tolerance but also with mild IFG or decreased K_g. 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: AIR_g, 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 Système International (SI) units and conversion factors for many substances.

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Obesity has long been recognized to be associated with insulin resistance; however, the majority of obese individuals maintain normal glucose tolerance. The major reason for this maintenance of glucose tolerance is a compensatory increase in insulin secretion in response to insulin resistance, such that both basal insulin levels and stimulated insulin responses are increased (1–3). The relationship between insulin sensitivity and fasting insulin and that between insulin sensitivity and the insulin response to intravenous glucose have been demonstrated to be hyperbolic in nature compatible with a classic feedback loop (4,5).

This hyperbolic relationship between insulin sensitivity and the acute insulin response to glucose (AIR_g) was first demonstrated in humans in young healthy subjects (5). Based on this hyperbolic function, the product of these two variables is a constant that is frequently called the disposition index (DI) and provides a measure of β -cell function. Calculation of the DI has been performed using data in subjects at high risk of developing diabetes (6–8) and to assess the impact of interventions on β -cell function (9,10). In these cross-sectional and longitudinal studies, many subjects demonstrated reduced glucose tolerance. While the DI was calculated in these population groups, the existence of the hyperbolic relationship that allows for this calculation under conditions of reduced glucose tolerance was not demonstrated but rather just assumed.

Thus, we sought to determine whether the hyperbolic relationship between insulin sensitivity and AIR_g exists in groups of individuals who do not have normal glucose metabolism. In addition, we addressed the question as to what impact the fasting glucose level had on insulin sensitivity and β -cell function.

RESEARCH DESIGN AND METHODS

We analyzed baseline data from 220 subjects with fasting plasma glucose (FPG) <6.1 mmol/L who

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 AIR_g value was highly influential with a Cook's distance that was >50 times the average distance and was over three times higher than the second highest value. This subject was therefore excluded from regressions that involved AIR_g . All subjects gave written informed consent to participate in the study, which was approved by the human subjects review committee at 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, AIR_g , 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_i) was calculated using Bergman's minimal model of glucose kinetics (13). AIR_g 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_g) was calculated as the slope of the natural log of glucose from 10 to 19 min, expressed as percent change per minute. β -Cell function was determined as the DI, which was calculated as the product of S_i and AIR_g .

Data analysis and statistical approach

To determine whether the relationship between the dependent (fasting insulin or AIR_g) and independent (S_i) variable was hyperbolic ($x \times y = \text{constant}$), we esti-

mated the natural logarithm (\ln) of fasting insulin or AIR_g as a linear function of $\ln(S_i)$ 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_i , AIR_g , and fasting insulin were based on the day-to-day coefficients of variation for these measures in our laboratory (16.9% for S_i , 20.6% for AIR_g , 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 \pm 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_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_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 \pm SE, unless otherwise specified. A two-sided $P < 0.05$ 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/m²). Further, they had broad ranges of fasting insulin (18–276 pmol/l), S_i ($0.7\text{--}25.3 \times 10^{-5} \text{ min}^{-1}/\text{pmol/l}$), AIR_g (32–2638 pmol/l), DI ($245\text{--}6461 \times 10^{-5} \text{ min}^{-1}$), and K_g (0.6–3.9%/min).

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

For the entire cohort, there was a significant correlation between $\ln(S_i)$ and \ln (fasting insulin) ($r = -0.72$, $P < 0.001$) and between $\ln(S_i)$ and $\ln(\text{AIR}_g)$ ($r = -0.37$, $P < 0.001$). The slopes for these relationships were not significantly different from -1 [$\ln(S_i)$ vs. \ln (fasting insulin) slope = -0.96 ± 0.07 ; $\ln(S_i)$ vs. $\ln(\text{AIR}_g)$ 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 β -cell function

BMI and fasting insulin were higher and S_i , AIR_g , the DI, and K_g were lower in the IFG category (Table 1). The slope for the relationship between $\ln(S_i)$ 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 $\ln(S_i)$ 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

Fasting glucose range (mmol/l)			NFG	IFG	FPG Q1 (4.48–5.09)	FPG Q2 (5.09–5.33)	FPG Q3 (5.35–5.65)	FPG Q4 (5.65–6.07)	P values by ANOVA for glucose quartiles
<i>n</i>		156		63	55	55	55	54	
Age (years)		51.7 ± 0.8		53.3 ± 1.3	49.7 ± 1.2	52.3 ± 1.5	54.5 ± 1.5	52.3 ± 1.3	NS
BMI (kg/m ²)		25.5 ± 0.3		28.0 ± 0.5*	24.6 ± 0.5	26.0 ± 0.6	26.3 ± 0.5	28.0 ± 0.5	<0.001, 1 vs. 4; <0.05, 2 vs. 4
Fasting glucose (mmol/l)		5.2 ± 0.02		5.8 ± 0.02*	4.86 ± 0.02	5.21 ± 0.01	5.46 ± 0.01	5.83 ± 0.01	<0.001 for each
Fasting insulin (pmol/l)		56.1 ± 2.7		70.9 ± 4.7†	45.2 ± 2.8	61.0 ± 5.6	65.5 ± 5.0	70.1 ± 4.8	<0.001, 1 vs. 4; <0.05, 1 vs. 3
S _i (×10 ^{−5} min ^{−1} /pmol/l)		7.19 ± 0.33		4.79 ± 0.30*	9.04 ± 0.69	6.37 ± 0.40	5.76 ± 0.43	4.79 ± 0.33	≤0.001, 1 vs. 2, 3, and 4
AIR _g (pmol/l)		356 ± 16		300 ± 44*	341 ± 25	363 ± 29	346 ± 25	311 ± 50	NS
DI (×10 ^{−5} min ^{−1})		2,215 ± 104		1,132 ± 93*	2,623 ± 186	2,028 ± 168	1,798 ± 160	1,151 ± 98	≤0.001, 1 vs. 3 and 4 and 2 vs. 4; <0.05, 1 vs. 2 and 3 vs. 4
K _g (%/min)		1.83 ± 0.05		1.37 ± 0.04*	1.98 ± 0.01	1.76 ± 0.08	1.66 ± 0.06	1.38 ± 0.05	<0.001, 1 and 2 vs. 4; <0.05 1 vs. 3 and 3 vs. 4
K _g range (%/min)					K _g Q1 (0.57–1.32)	K _g Q2 (1.33–1.59)	K _g Q3 (1.60–1.94)	K _g Q4 (1.95–3.9)	
<i>n</i>		—		—	55	55	55	54	
Age (years)		—		—	54.3 ± 1.3	53.9 ± 1.5	49.2 ± 1.4	51.5 ± 1.4	NS
BMI (kg/m ²)		—		—	26.9 ± 0.6	26.5 ± 0.6	26.3 ± 0.5	25.2 ± 0.4	NS
Fasting glucose (mmol/l)		—		—	5.55 ± 0.05	5.44 ± 0.04	5.25 ± 0.05	5.14 ± 0.05	<0.001, 1 vs. 3 and 4 and 2 vs. 4; <0.05, 2 vs. 3
Fasting insulin (pmol/l)		—		—	61.8 ± 5.9	64.1 ± 5.0	59.8 ± 4.5	55.8 ± 3.7	NS
S _i (×10 ^{−5} min ^{−1} /pmol/l)		—		—	5.87 ± 0.54	5.51 ± 0.43	6.51 ± 0.50	8.13 ± 0.57	<0.01, 1 and 2 vs. 4
AIR _g (pmol/l)		—		—	207 ± 16	274 ± 19	390 ± 47	493 ± 30	<0.001, 1 and 2 vs. 4; <0.05 1 and 2 vs. 3
DI (×10 ^{−5} min ^{−1})		—		—	999 ± 81	1,252 ± 72	1,974 ± 101	3,416 ± 180	<0.001 for all except NS for 1 vs. 2
K _g (%/min)		—		—	1.11 ± 0.02	1.47 ± 0.01	1.75 ± 0.01	2.48 ± 0.07	

Data are means \pm SE. * $P \leq 0.001$ vs. NFG by *t* test; † $P = 0.005$.

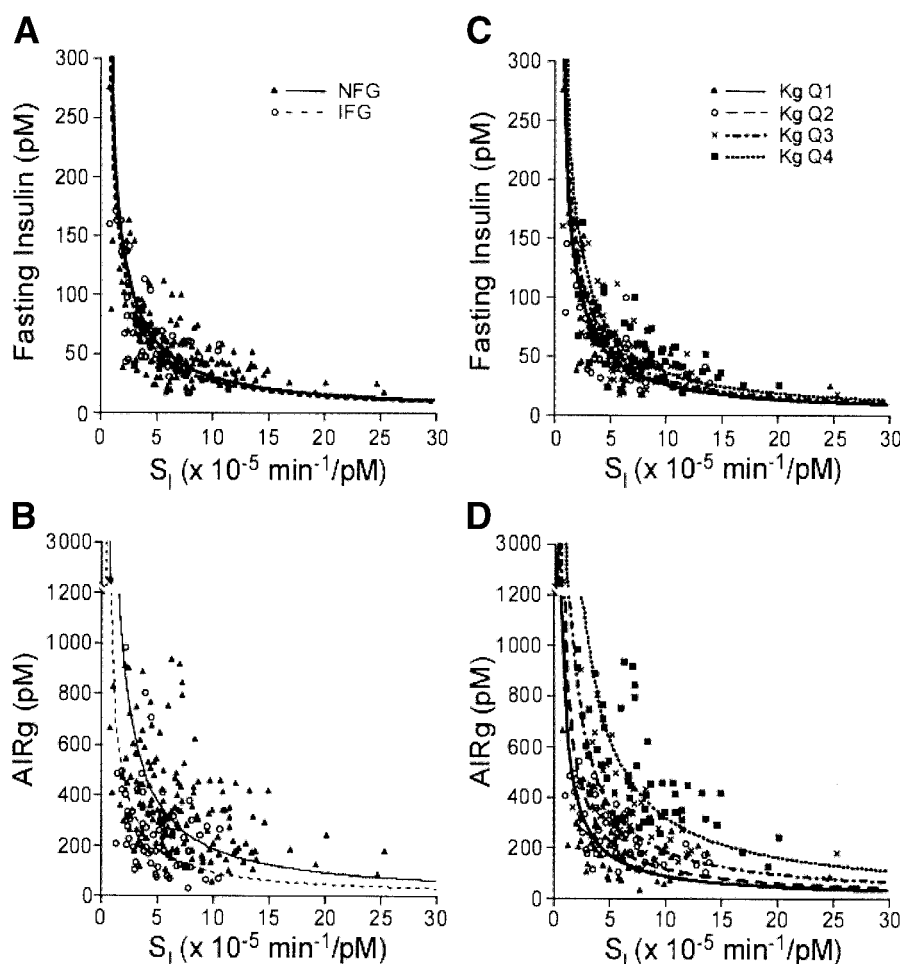


Figure 1—The hyperbolic relationship between fasting insulin and S_1 (A) and AIR_g and S_1 (B) for NFG (FPG <5.6 mmol/L, $n = 156$) and for IFG (5.6–6.1 mmol/L, $n = 63$) and the hyperbolic relationship between fasting insulin and S_1 (C) and AIR_g and S_1 (D) by K_g quartile. The hyperbolic relationship between AIR_g and S_1 is left and downward shifted in the IFG group compared with the NFG group and is progressively leftward and downward shifted with decreasing K_g , consistent with decreased β -cell function.

The slope for the relationship between $\ln(S_1)$ and $\ln(AIR_g)$ for NFG was -0.71 ± 0.11 and that for IFG was -1.30 ± 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_1 and AIR_g was leftward and downward shifted in the IFG group consistent with a decrease in β -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_1 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_1 , resulting in a progressive decrease in the DI (Table 1). These findings were confirmed by linear regression with both S_1 [$\ln(S_1)$ 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_1 , AIR_g , and the DI declined. In fact, the greatest decrease in S_1 occurred between quartiles 1 and 2, where all subjects had fasting glucose in the normal range.

Effect of intravenous glucose tolerance on the hyperbolic relationships between insulin sensitivity and fasting insulin and insulin sensitivity and AIR_g

Subjects were divided into quartiles based on K_g , with group characteristics presented in Table 1. The groups did not differ by age, BMI, or fasting insulin, while decreasing K_g was associated with increasing FPG and decreasing S_1 , AIR_g , and DI.

The slopes for the relationship between $\ln(S_1)$ and $\ln(\text{fasting insulin})$ for each of the K_g quartiles were Q1: -0.99 ± 0.12 , Q2: -0.92 ± 0.10 , Q3: -1.17 ± 0.23 , and Q4: -1.03 ± 0.18 . There was no difference in slope for the relationship between $\ln(S_1)$ and $\ln(\text{fasting insulin})$ between K_g quartiles. However, a significant increase in intercept was present 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 $\ln(S_1)$ and $\ln(AIR_g)$ for each K_g quartile were Q1: -0.79 ± 0.18 , Q2: -0.61 ± 0.07 , Q3: -0.92 ± 0.20 , and Q4: -0.72 ± 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_1 and AIR_g shifted progressively leftward and downward with decreasing K_g , consistent with decreasing β -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 $\ln(S_1)$ and $\ln(\text{fasting insulin})$ and between $\ln(S_1)$ and $\ln(AIR_g)$ between subjects with NFG and those with mild IFG (FPG between 5.6 and 6.1 mmol/L;

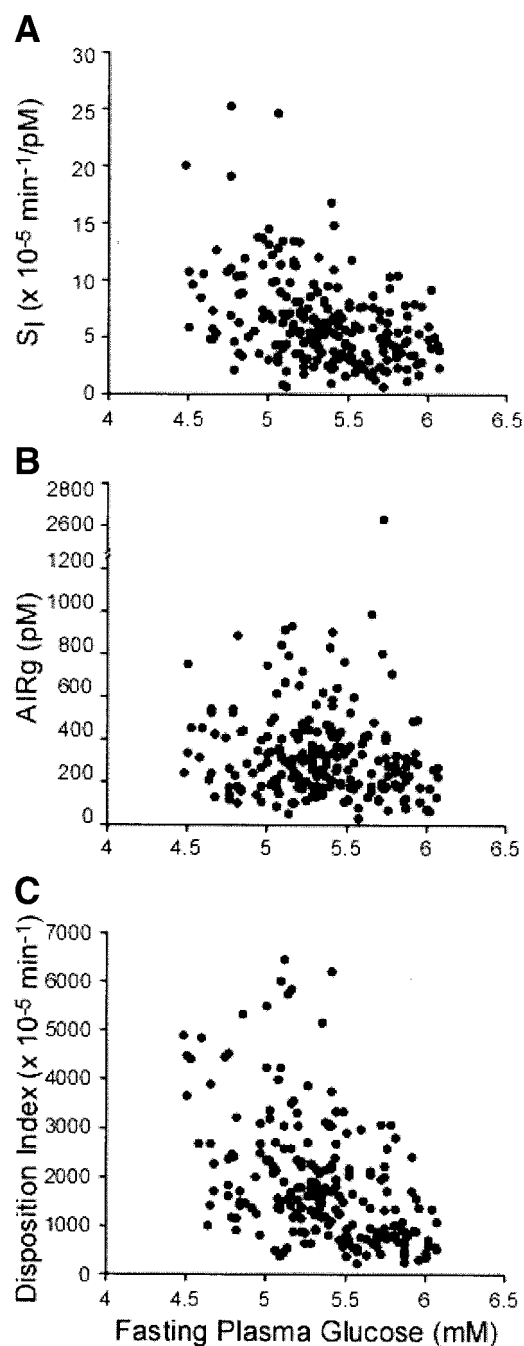


Figure 2—Plots of fasting plasma glucose versus S_I (A), AIR_g (B), and the DI (C) for the entire cohort demonstrate progressive decreases in both S_I and the DI as fasting glucose increases, even in NFG subjects.

100 and 110 mg/dl) and between subjects when divided into quartiles by intravenous glucose tolerance (K_g). These findings support the hypothesis that the relationship between insulin sensitivity and AIR_g is similar in subjects with normal and abnormal glucose metabolism. Based on a hyperbolic relationship, use of the DI (when considering S_I and AIR_g) as a measure of β -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 β -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 AIR_g than a lean insulin-sensitive subject. However, based on the inverse relationship between insulin sensitivity and AIR_g , calculation of the DI demon-

strates 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 β -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 β -cell function. With increasing fasting glucose, S_I decreases progressively but AIR_g 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 β -cell function occur. This is in contrast to the findings of Godsland et al. (18) who observed that AIR_g 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 β -cell function will not be useful in groups of subjects lacking a first-phase insulin response. It is well recognized that AIR_g 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 S_I and AIR_g exists at higher glucose levels or in subjects with diabetes. However, we believe it would be unlikely given the lack of an AIR_g 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 (AIR_{max}) (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 S_i and AIR_{max} 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 $\ln(S_i)$ versus $\ln(\text{AIR}_g)$ 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 $\ln(\text{insulin sensitivity})$ versus $\ln(\text{fasting insulin})$ 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 S_i and both fasting insulin and AIR_g 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 AIR_g 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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