Insulin Secretion and Action in Subjects With Impaired Fasting Glucose and Impaired Glucose Tolerance
Results From the Veterans Administration Genetic Epidemiology Study

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This study was conducted to observe changes in insulin secretion and insulin action in subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). A total of 319 subjects were studied with an oral glucose tolerance test (OGTT). Fasting plasma glucose and insulin concentrations were measured at baseline and every 30 min during the OGTT. Fifty-eight subjects also received a euglycemic-hyperinsulinemic clamp. Insulin sensitivity was calculated as the total glucose disposal (TGD) during the last 30 min of the clamp. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting plasma glucose and insulin concentrations. Subjects with IFG had TGD similar to normal glucose-tolerant subjects, while subjects with IGT and combined IFG/IGT had significantly reduced TGD. HOMA-IR in subjects with IFG was similar to that in subjects with combined IFG/IGT and significantly higher than HOMA-IR in subjects with IGT or NGT. Insulin secretion, measured by the insulinogenic index (ΔI₉₋₃₀/ΔG₉₋₃₀) and by the ratio of the incremental area under the curve (AUC) of insulin to the incremental AUC of glucose (0–120 min), was reduced to the same extent in all three glucose-intolerant groups. When both measurements of β-cell function were adjusted for severity of insulin resistance, subjects with IGT and combined IFG/IGT had a significantly greater reduction in insulin secretion than subjects with IFG. Subjects with IGT and IFG have different metabolic characteristics. Differences in insulin sensitivity and insulin secretion may predict different rates of progression to type 2 diabetes and varying susceptibility to cardiovascular disease. Diabetes 55:1430–1435, 2006

Impaired glucose intolerance (IGT) is an intermediate state in the transition from normal glucose tolerance (NGT) to type 2 diabetes (1). Subjects with IGT, although still normoglycemic, manifest the dual defects that are characteristic of type 2 diabetes: reduced insulin sensitivity and impaired β-cell function (2). As a result, they are at high risk for progression to type 2 diabetes, with an annual conversion rate of 5–10%, depending upon the ethnic group that is studied (3–7).

In 1997, the American Diabetes Association introduced another intermediate state, impaired fasting glucose (IFG) (8), in the transition of glucose homeostasis from NGT to type 2 diabetes. IFG was meant to be analogous to IGT, since subjects with IFG also are at high risk for progression to type 2 diabetes. In epidemiological studies (3–7), subjects with isolated IGT and isolated IFG had similar risk for progression to type 2 diabetes. However, only 45% of subjects with IFG had IGT; conversely, <25% of subjects with IGT had IFG (4,5,9–13). The partial overlap between IFG and IGT suggests that different pathophysiological mechanisms contribute to the disturbances in glucose homeostasis. In some studies, insulin resistance was reported to be the primary abnormality in subjects with IFG, while IGT was more associated with impaired β-cell function (14–21). However, other investigators have reported completely opposite results (22–26). In part, the divergent results may be explained by the failure to utilize more sophisticated techniques to quantitate insulin sensitivity and insulin secretion. In this study, we used the oral glucose tolerance test (OGTT) and euglycemic-hyperinsulinemic clamp to examine the presence of impaired insulin secretion and insulin resistance in isolated IFG, isolated IGT, and combined IFG/IGT.

RESEARCH DESIGN AND METHODS
The participants included 319 subjects of Mexican-American descent who were part of the San Antonio Veterans Administration Genetic Epidemiology Study. In the Veterans Administration Genetic Epidemiology Study, Mexican-American families with one diabetic and one nondiabetic parent and two siblings with type 2 diabetes were recruited through advertising within the medical center and in local newspapers. Subjects responding to the advertisement were screened with a 75-g OGTT. This study reports on 319 subjects with NGT, IFG, and IGT, 58 of whom also had a euglycemic insulin clamp study. Based on the OGTT, subjects were classified as having NGT (fasting glucose <5.6 mmol/l and 2-h glucose <7.8 mmol/l, n = 117), IGT (fasting glucose <5.6 mmol/l and 2-h glucose ≥7.8 mmol/l), IFG (fasting glucose ≥5.6 mmol/l and 2-h glucose <7.8 mmol/l, n = 39), and combined IFG/IGT (fasting glucose ≥5.6 mmol/l and 2-h glucose ≥7.8 mmol/l, 37 subjects). The study was performed in compliance with the American Health Care Personnel Privacy Rule.
mmol/l and 2-h glucose between 7.8 and 11.1 mmol/l, n = 93), IFG (fasting glucose between 5.6 and 7.0 mmol/l and 2-h glucose <7.8 mmol/l, n = 32), or combined glucose intolerant (CGI) (fasting glucose between 5.6 and 7 mmol/l and 2-h glucose between 7.8 and 11.1 mmol/l, n = 77), according to the American Diabetes Association criteria (8,27).

All subjects had normal liver, cardiopulmonary, and kidney function as determined by medical history, physical examination, screening blood tests, electrocardiogram, and urinalysis. No normal glucose-tolerant, IFG, or impaired glucose-tolerant subject was taking any medication known to affect glucose tolerance. Body weight was stable (±2 kg) for at least 3 months before study in all subjects. The study protocol was approved by the institutional review board of the University of Texas Health Science Center, San Antonio, and informed written consent was obtained from all subjects before their participation. All studies were performed at the general clinical research center of the University of Texas Health Science Center at 0800 following a 10- to 12-h overnight fast.

OGTT. Before the start of the OGTT, a small polyethylene catheter was placed into an antecubital vein and blood samples were collected at −30, −15, 0, 30, 60, 90, and 120 min for the measurement of plasma glucose and insulin concentrations. On the day of the OGTT, waist circumference was determined at the narrowest part of the torso (28).

Euglycemic insulin clamp. Before the start of the insulin clamp (29), a catheter was placed into an antecubital vein for the infusion of all test substances. A second catheter was inserted retrogradely into a vein on the dorsum of the hand, and the hand was placed into a thermoregulated box heated to 70°C. At 0800, all subjects received a primed (25 µCi)-continuous (0.25 µCi/min) infusion of 3-[3H]glucose (DuPont NEN Life Science Products, Boston, MA), which was continued for 2 h. After the basal tracer equilibration period, subjects received a primed-continuous insulin infusion at the rate of 240 pmol (40 mU) · min⁻¹ · m⁻² for 120 min. During the last 30 min of the basal equilibration period, plasma samples were taken at 5- to 10-min intervals for the determination of plasma glucose and insulin concentrations and triated glucose radioactivity. During the insulin infusion, plasma glucose concentration was measured every 5 min, and a variable infusion of 20% glucose was adjusted, based on the negative feedback principle, to maintain the plasma glucose concentration at each subject’s fasting plasma glucose level with a coefficient of variation <5%. Plasma samples were collected every 15 min from 0 to 90 min and every 5–10 min from 90 to 120 min for the determination of plasma glucose and insulin concentrations and triated glucose specific activity.

Calculations. Following an overnight fast, steady-state conditions prevailed, and endogenous glucose production (EGP) was calculated as the tritiated glucose infusion rate (dpm/min) divided by the plasma tritiated glucose specific activity (dpm/mg). During the insulin clamp, non–steady-state conditions for tritiated glucose specific activity prevailed, and the rate of glucose appearance (Ra) was calculated with Steele’s equation (30). The rate of residual EGP during the insulin clamp was calculated by subtracting the rate of exogenous glucose infusion rate from the tracer-derived Ra. The insulin-stimulated rate of total glucose disposal (TGD) was calculated by adding the rate of residual EGP to the exogenous glucose infusion rate.

Insulin sensitivity indexes were also calculated from OGTT using the Matsuda (31), HOMA-IR (32), ISIest (33), and oral glucose insulin sensitivity (OGIS) (34) indexes. The insulinogenic index or incremental area under the curve of insulin (ΔI[AUC]) divided by the incremental area under the curve of glucose (ΔG[AUC]) was calculated during the 0- to 30-min (early) and 0- to 120-min (total) time period of the OGTT. To evaluate β-cell function, the insulin secretion/sensitivity index (so-called disposition index) was calculated as ΔI[AUC]/ΔG[AUC]/steady-state plasma insulin/TGD or ΔI[AUC]/ΔG[AUC] × Matsuda index. Incremental AUCs of plasma glucose and insulin during the OGTT were calculated according the trapezoid rule.

Analytical techniques. Plasma glucose was measured by the glucose oxidase reaction (Glucose Oxidase Analyzer; Beckman, Fullerton, CA). Plasma insulin concentration was measured by a radioimmunoassay (Linco Research, St. Louis, MO). Plasma 3-[3H]glucose radioactivity was measured in Somogyi precipitates.

Statistical analysis. Data are presented as the mean ± SD. *P < 0.01; †P < 0.0001 by ANOVA, indicating that the means of the four groups are significantly different.

RESULTS
Table 1 presents the anthropometric and metabolic characteristics of the study groups. In general, subjects with IFG/IGT/CGI were slightly more obese than subjects with NGT. Subjects with IFG had a higher percentage of being male and higher total/LDL cholesterol concentrations. Subjects with high fasting plasma glucose concentrations (IFG and CGI) had significantly higher fasting plasma triglyceride and insulin concentrations than subjects with NGT.

Plasma glucose and insulin concentrations. Plasma glucose and insulin concentrations during the OGTT are displayed in Fig. 1. Compared with normal glucose-tolerant subjects, individuals with IGT had a small but significant increase in fasting plasma glucose concentration, but the 2-h plasma glucose and the incremental glucose AUC during the OGTT were markedly increased by 42 and 68%, respectively. Although the incremental insulin AUC in the impaired glucose-tolerant group was similar to that in the normal glucose-tolerant group, the time course of insulin response was very different (Fig. 1). Thus, the plasma insulin response rose progressively from 60 to 120 min in the impaired glucose-tolerant group, while it declined toward the baseline after 60 min in the normal glucose-tolerant group. By definition, subjects with IFG had significantly elevated fasting plasma glucose compared with
normal and impaired glucose-tolerant subjects, and their fasting plasma insulin concentration was higher than the value in both NGT and IGT. The incremental glucose AUC during the OGTT (97 ± 36 mg · dl⁻¹ · h⁻¹) in the IFG group was intermediate between that of the normal (74 ± 34 mg · dl⁻¹ · h⁻¹, P < 0.0001) and impaired (124 ± 31 mg · dl⁻¹ · h⁻¹, P < 0.0001) glucose-tolerant groups. However, the 2-h plasma glucose concentration in the IFG group had returned to values observed in NGT (119 vs. 114 mg/dl, P = NS) and was markedly less than in the impaired glucose-tolerant group (162 mg/dl). The incremental insulin AUC was significantly reduced in IFG compared with both IGT and NGT. Subjects with CGI had elevated plasma glucose and insulin concentrations, similar to those with IFG, and elevated incremental glucose and insulin AUC, similar to IGT. Thus, individuals with CGI shared the characteristics of both IFG and IGT.

**Indexes of insulin resistance.** Insulin resistance, calculated by HOMA-IR, was significantly higher in subjects with elevated fasting plasma glucose concentrations (IFG and CGI) compared with subjects with normal fasting glycaemia (NGT and IGT). However, insulin sensitivity, calculated by the Matsuda, ISIest, and OGIS indexes, were significantly reduced in the three glucose-intolerant groups (IFG, IGT, and CGI) compared with subjects with NGT (Table 2). The three indexes were virtually identical in IFG and impaired glucose-tolerant groups.

**Direct measurement of insulin sensitivity.** A total of 58 subjects received in a euglycemic-hyperinsulinemic clamp: 29 subjects with NGT, 10 subjects with IFG, 9 subjects with IGT, and 10 subjects with CGI. Insulin-stimulated total-body glucose disposal was similar in subjects with NGT and IFG, and it was reduced by 42 and 48%, respectively, in subjects with IGT and CGI compared with NGT (Table 2, Fig. 2). The basal hepatic insulin resistance index (hepatic glucose production [HGP] × fasting plasma insulin [FPI]) was significantly increased by 35–40% in IFG and CGI compared with NGT. There was a small, but significant (11%), increase in the hepatic insulin resistance index in IGT (Fig. 2).

**Correlation between OGTT- and clamp-derived insulin sensitivity indexes.** Table 3 presents the simple Pearson’s correlations between OGTT-derived insulin sensitivity indexes and TGD measured with the insulin clamp and basal hepatic insulin resistance index (HGP × FPI). HOMA-IR correlated more strongly with the basal hepatic insulin resistance index than with TGD, while the Matsuda, Stumvoll, and OGIS indexes correlated more strongly with TGD than with the basal hepatic insulin resistance index.

**Insulin secretion.** Insulin secretion during the 120-min OGTT, measured by ΔI(AUC)/ΔG(AUC), was reduced sim-

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**TABLE 2**

<table>
<thead>
<tr>
<th>Indexes of insulin sensitivity and insulin secretion in the different glucose-intolerant groups</th>
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<tbody>
<tr>
<td>NGT</td>
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<tr>
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</tr>
<tr>
<td>ΔG(AUC) (mg · dl⁻¹ · h⁻¹)</td>
</tr>
<tr>
<td>ΔI(AUC) (µU · ml⁻¹ · h⁻¹)</td>
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<tr>
<td>ΔI(AUC)/ΔG(AUC)*</td>
</tr>
<tr>
<td>I₀−30/G₀−30 (µU/ml per mg/dl)</td>
</tr>
<tr>
<td>HOMA-IR*</td>
</tr>
<tr>
<td>Matsuda index*</td>
</tr>
<tr>
<td>ISIest†</td>
</tr>
<tr>
<td>OGIS*</td>
</tr>
<tr>
<td>Basal EGP (mg · kg⁻¹ · min⁻¹)</td>
</tr>
<tr>
<td>Basal EGP × FPI*</td>
</tr>
<tr>
<td>TGD/SSPI × 100*</td>
</tr>
<tr>
<td>(ΔI₀−30/ΔG₀−30) × Matsuda index*</td>
</tr>
<tr>
<td>(ΔI₀−30/ΔG₀−30) (TGD/SSPI) × 100*</td>
</tr>
<tr>
<td>ΔI(AUC)/ΔG(AUC) × (TGD/SSPI)</td>
</tr>
</tbody>
</table>

Data are means ± SD. The Matsuda index of insulin sensitivity was calculated according to (31). The ISIest of insulin sensitivity was calculated according to (33). The OGIS index of insulin sensitivity was calculated according to (34). *P < 0.01; †P < 0.001 by ANOVA, indicating that the means of the four groups are significantly different. ΔG(AUC), incremental AUC of glucose during the OGTT; ΔI(AUC), incremental AUC of insulin during the OGTT; SSPI, steady-state plasma insulin during the last 30 min of the insulin clamp.

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IFG subjects was similar to that in normal glucose-tolerant subjects, while insulin-mediated glucose disposal was markedly reduced in subjects with IGT and CGI. Since >80–90% of glucose disposal during the euglycemic-hyperinsulinemic clamp occurs in skeletal muscle (29,35), subjects with IGT and CGI are characterized by moderate-to-severe muscle insulin resistance. In contrast, muscle insulin sensitivity was normal in subjects with IFG. When HOMA-IR was used to derive an index of insulin resistance, IFG subjects were found to be markedly insulin resistant compared with subjects with NGT, while impaired glucose-tolerant subjects had minimally (not significantly) reduced insulin sensitivity. Using HOMA-IR, CGI subjects were as insulin resistant as IFG individuals. This apparent discrepancy between HOMA-IR and the insulin clamp–derived measurement of insulin resistance does not reflect methodological inconsistencies but rather the different underlying physiological processes that are being quantitated. The HOMA-IR index is derived from the product of the fasting plasma glucose and insulin concentrations (32). Since HGP is the primary determinant of the fasting plasma glucose concentration (36), and the fasting plasma insulin concentration is the primary regulator of HGP (37), the product of fasting plasma glucose and FPI primarily reflects hepatic insulin resistance. This is confirmed in the subgroup of subjects who received tritiated glucose to measure HGP. In this subgroup of subjects, HOMA-IR correlated more strongly with HGP × FPI than with TGD. In the IFG group, the hepatic insulin resistance index (HGP × FPI) was increased, while in IGT it was only minimally elevated. We have previously shown that there is a 70% concordance between muscle insulin resistance and liver insulin resistance in the same subject (38). Thus, we interpret our results to indicate that individuals with IFG are primarily characterized by hepatic insulin resistance, while subjects with IGT mainly have muscle insulin resistance. These conclusions are consistent with previously published results. Festa et al. (24) and Weyer et al. (23) have reported that subjects with isolated IGT had a significant reduction in insulin sensitivity, as measured with an intravenous glucose tolerance test and insulin clamp. On the other hand, the product of EGP × FPI was markedly increased in subjects with IFG (23). Fasting hyperinsulinemia has been observed in subjects with IFG in all (14–17,19,23–26) but one (22) study. The higher product of fasting plasma glucose × FPI in individuals with IFG indicates the presence of hepatic insulin resistance.

Individuals with CGI manifested marked fasting hyperinsulinemia and had both reduced TGD during the insulin clamp and a high HOMA-IR. The former reflects muscle insulin resistance, while the later (HOMA-IR) is indicative of hepatic insulin resistance. Thus, subjects with CGI had both muscle and liver insulin resistance, and both defects were quite severe. The combination of severe liver and muscle insulin resistance in subjects with CGI may explain their higher risk (twofold greater than IGT and IFG) for progression to type 2 diabetes in prospective epidemiological studies (3–7). The Matsuda index of insulin sensitivity (31) contains the fasting plasma glucose × FPI (index of hepatic insulin resistance) and the mean plasma glucose multiplied by the mean plasma insulin during the OGTT (index of muscle insulin resistance). Therefore, it is not surprising that it more strongly correlates with TGD than HOMA-IR, and it was reduced to a significantly greater extent in CGI compared with both IGT and IFG. Similarly, ISI\textsuperscript{est} and OGIS indexes, which are also derived from

DISCUSSION
The present results demonstrate that subjects with IGT and IFG have distinct pathophysiological disturbances. During the euglycemic-hyperinsulinemic clamp, TGD in

![Graph A](image)

**FIG. 2.** Total-body (primarily reflects muscle) insulin sensitivity (A) measured with the insulin clamp and the hepatic insulin sensitivity index (B) measured with tritiated glucose in the different glucose-intolerant groups. SSPI, steady-state plasma insulin concentration during the last 30 min of the insulin clamp.

TABLE 3
Pearson’s correlation coefficients between OGTT-derived insulin sensitivity indexes and liver and muscle insulin sensitivity measured during the clamp

<table>
<thead>
<tr>
<th>Correlation with</th>
<th>Correlation with</th>
</tr>
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<tbody>
<tr>
<td>TGD/SSPI</td>
<td>EGP × FPI</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>−0.564 (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Matsuda index</td>
<td>0.688 (P &lt; 0.0001)</td>
</tr>
<tr>
<td>ISI\textsuperscript{est}</td>
<td>0.674 (P &lt; 0.0001)</td>
</tr>
<tr>
<td>OGIS</td>
<td>0.566 (P &lt; 0.0001)</td>
</tr>
</tbody>
</table>

HOMA-IR index was calculated from fasting plasma glucose and insulin concentrations during the OGTT. The hepatic insulin sensitivity index was calculated using the fasting plasma insulin concentration measured on the day of the insulin clamp. SSPI, steady-state plasma insulin concentration during the last 30 min of the insulin clamp.
plasma glucose and insulin concentrations during the OGTT, displayed a greater correlation with TGD than with liver insulin resistance (HOMA-IR).

The early-phase (0–30 min) insulinogenic index was diminished in all three glucose-intolerant groups. However, when expressed as ΔI0–30/ΔG0–30/IR, subjects with IGT and CGI had a greater reduction in insulin secretion than subjects with IFG. Similarly, ΔI0–120/ΔG0–120/IR was more severely reduced in IGT and CGI compared with IFG. Previous studies, which have measured insulin secretion with the hyperglycemic clamp (17,20) and intravenous glucose tolerance tests (23,24), consistently reported a 25–50% reduction in first- and second-phase insulin secretion in subjects with IGT compared with NGT. Since, in all of the above studies (17,20,23,24), subjects with IGT were insulin resistant compared with NGT, expression of first- and second-phase insulin secretion in relation to insulin resistance would have yielded a more profound reduction in insulin secretion in subjects with IGT, as we have previously reported (21). Unfortunately, no study has directly measured first- and second-phase insulin secretion with the hyperglycemic clamp and compared the results in subjects with IFG and IGT. Several studies have used the intravenous glucose tolerance test to measure the acute insulin response in IFG subjects (23,24) and observed a significant reduction in the absolute magnitude of acute insulin response compared with subjects with NGT. However, the insulin secretory response was not related to the severity of insulin resistance.

The metabolic characteristics described above (summarized in Table 2) help to explain the plasma glucose profile following ingestion of glucose load or mixed meal in individuals with IGT, IFG, and CGI. In subjects with IGT, the combination of deficient insulin secretion plus muscle insulin resistance results in less efficient disposal of the glucose load during the OGTT. As a result, the plasma glucose concentration continues to increase after 60 min and remains elevated at 120 min (Fig. 1). This is in contrast to normal glucose-tolerant subjects in whom the plasma glucose concentration peaks at 30 min and returns to the mean basal value at 120 min. Subjects with IFG start with a high fasting plasma glucose level (due to hepatic insulin resistance), but the incremental rise in plasma glucose concentration at 30–60 min is only slightly greater than NGT (Fig. 1), and at 120 min the plasma glucose concentration returns to a value similar to that in NGT. Consequently, the increment in plasma glucose concentration above baseline from 0 to 120 min was only slightly greater than in the normal glucose-tolerant group. This is explained by normal muscle insulin sensitivity (measured with the insulin clamp), which, even in the face of a modest defect in insulin secretion, is able to maintain a near-normal incremental plasma glucose response during the OGTT. Individuals with CGI start with a high fasting plasma glucose concentration because of hepatic insulin resistance and have the greatest rise in plasma glucose concentration during the OGTT because of muscle (and hepatic) insulin resistance and impaired insulin secretion.

In summary, a clearer understanding of the pathophysiological abnormalities that characterize varying glucose-intolerant groups provides insights into the development of interventions to slow/halt the progression to type 2 diabetes. Subjects with IFG, who predominantly manifest liver insulin resistance, are most likely to benefit from agents that improve hepatic insulin sensitivity, such as metformin, while subjects with IGT, who predominantly have muscle insulin resistance combined with severely impaired insulin secretion, are more likely to respond to agents that improve skeletal muscle insulin resistance, such as a peroxisome proliferator-activated receptor-γ agonist, in combination with an insulin secretagogue such as a glucagon-like peptide-1 derivative.

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REFERENCES

15. Guerrero-Romero F, Rodriguez-Moran M: Impaired glucose tolerance is a
more advanced stage of alteration in the glucose metabolism than impaired fasting glucose. *J Diab Comp* 15:34–37, 2001


20. Pimenta WP, Santos ML, Cruz NS, Aragon FF, Padovani CR, Gerich JE: Brazilian individuals with impaired glucose tolerance are characterized by impaired insulin secretion. *Diabetes Metab* 28:468–476, 2002


23. Weyer C, Bogardus C, Pratley R: Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes* 48:2197–2203, 1999


