To characterize the defects in β-cell function in subjects with impaired fasting glucose (IFG) and compare the results to impaired glucose tolerance (IGT) and normal glucose tolerance (NGT) subjects, β-cell glucose sensitivity and rate sensitivity during the oral glucose tolerance test were measured with the model by Mari in 172 Mexican Americans. A subgroup (n = 70) received a 2-h hyperglycemic clamp (+125 mg/dL), and first- and second-phase insulin secretion were quantitated. Compared with NGT, subjects with IFG and IGT manifested a decrease in β-cell glucose sensitivity; IFG subjects, but not IGT subjects, had decreased β-cell rate sensitivity. In IFG subjects, the defect in β-cell glucose sensitivity was time dependent, began to improve after 60 min, and was comparable to NGT after 90 min. The incremental area under the plasma C-peptide concentration curve during the first 12 min of the hyperglycemic clamp (ΔC-pep[AUC]0–12) was inversely related with the increase in FPG concentration (r = −0.36, r = 0.001), whereas ΔC-pep[AUC]15–120 positively correlated with FPG concentration (r = 0.29, r < 0.05). When adjusted for the prevailing level of insulin resistance, first-phase insulin secretion was markedly decreased in both IFG and IGT, whereas second-phase insulin secretion was decreased only in IGT. These results demonstrate distinct defects in β-cell function in IFG and IGT. Diabetes 61:447–453, 2012

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are intermediate states in the transition in glucose tolerance from normal to overt diabetes. IFG was originally introduced by the American Diabetes Association to be analogous to IGT (1). Although subjects with isolated IFG and isolated IGT have a similarly impaired ability of β-cell function in IFG has been extensively studied (14–17,19,20,23). The aim of the current study was to characterize the defects in β-cell function in IGT subjects can be explained by an intrinsic defect in β-cell glucose sensitivity to the ambient plasma glucose level. Similarly, studies with the intravenous glucose tolerance test have demonstrated impaired acute insulin response in IGT (14,17,19,20). In addition, Ferrannini and colleagues (13,22) have demonstrated that the defect in β-cell function in IGT subjects was inversely related with the increase in FPG concentration (r = −0.4, r = 0.01), whereas ΔC-pep[AUC]15–120 positively correlated with FPG concentration (r = 0.29, r < 0.05). When adjusted for the prevailing level of insulin resistance, first-phase insulin secretion was markedly decreased in both IFG and IGT, whereas second-phase insulin secretion was decreased only in IGT. These results demonstrate distinct defects in β-cell function in IFG and IGT. Diabetes 61:447–453, 2012

RESEARCH DESIGN AND METHODS

The participants were 172 subjects of Mexican-American descent who were part of the San Antonio Veterans Administration Genetic Epidemiology Study (VAGES) (9). In VAGES, Mexican-American subjects received a 75-g OGTT, and based on the OGTT, subjects were classified as having NGT, IFG, and IGT according to the American Diabetes Association criteria (1). This study reports on 172 subjects with NGT (n = 75), isolated IFG (n = 46), and isolated IGT (n = 48).

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

OGTT. Before the start of the OGTT, a polyethylene catheter was placed into an antecubital vein, and blood samples were collected at −30, −15, 0, 15, 30, 45, 60, 75, 90, 105, and 120 min for the measurement of plasma glucose, insulin,
and C-peptide concentrations. On the day of the OGTT, body weight, height, and waist circumference at the narrowest part of the torso were determined.

**Hyperglycemic clamp.** All subjects were offered a hyperglycemic clamp, but only a subgroup agreed to participate in a 2-h hyperglycemic clamp. Before the start of the clamp, a catheter was inserted into a vein for the infusion of glucose. 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. After obtaining three baseline samples, plasma glucose concentration was raised and maintained at 125 mg/dL above fasting.

After the clamp was started, a concomitant intravenous infusion of 30% glucose was started at a rate of 0.5 mg/kg/min and was increased by a variable amount to maintain a glucose concentration between 15 and 120 min (ΔG0–12) divided by the increment in plasma glucose concentration above the fasting level at the same time point (ΔISR/ΔG0–12). This ratio expresses glucose-stimulated insulin secretion (in pmol·min⁻¹·m⁻²) as the sum of two components: 1) β-cell glucose sensitivity and 2) rate sensitivity. First-phase insulin secretion during the hyperglycemic clamp was calculated as the incremental area under plasma C-peptide concentration between 0–12 min (ΔC-pep0–12) divided by the increment in plasma glucose concentration during the same time period. First-phase insulin secretion during the hyperglycemic clamp was calculated as the incremental area under plasma C-peptide concentration curve, and the ratio between the incremental area under the plasma insulin secretory rate and incremental area under the plasma glucose concentration was calculated as previously described (25). β-Cell glucose sensitivity, rate sensitivity, and the potentiation factor were calculated with the model by Mari (12,22). This model expresses glucose-stimulated insulin secretion (in pmol·min⁻¹·m⁻²) as the sum of two components: 1) β-cell glucose sensitivity and 2) rate sensitivity. First-phase insulin secretion during the hyperglycemic clamp was calculated as the incremental area under plasma C-peptide concentration between 0–12 min (ΔC-pep0–12) divided by the increment in plasma glucose concentration during the same time period. First-phase insulin secretion during the hyperglycemic clamp was calculated as the incremental area under plasma C-peptide concentration between 0–12 min (ΔC-pep0–12) divided by the increment in plasma glucose concentration during the same time period. First-phase insulin secretion during the hyperglycemic clamp was calculated as the incremental area under plasma C-peptide concentration between 0–12 min (ΔC-pep0–12) divided by the increment in plasma glucose concentration during the same time period.

Data are presented as the mean ± SE. Pearson correlation was used to assess the relationship between variables. To examine the predictors of first- and second-phase insulin secretion during the hyperglycemic clamp, we constructed a linear regression model with the first- and second-phase insulin secretion as the dependent variable and other variables as the independent variable. Similarly, the contribution of the first- and second-phase insulin secretion during the hyperglycemic clamp and glucose concentration, i.e., insulin sensitivity, to the incremental increase in plasma glucose concentration during the OGTT was assessed with a linear regression model with ΔG as the dependent variable and first- and second-phase insulin secretion and glucose concentration as the independent variable. For comparison between groups, Student t test was used. To compare the mean of more than two groups, ANOVA was used. Statistical significance was considered at P < 0.05.

**RESULTS**

The characteristics of the study participants are presented in Table 1. Subjects in the three groups had a similar BMI. NGT subjects were slightly younger than IFG and IGT subjects. As anticipated, there were more males with IFG.

Figure 1 depicts the plasma glucose concentration and ISR during the OGTT in NGT, IFG, and IGT subjects. The absolute incremental area under the ISR curve during the OGTT (ΔISR0–120) was similar in NGT, IFG, and IGT (13.6 ± 0.6, 11.5 ± 0.9, and 14.9 ± 0.9, respectively; P = nonsignificant). However, the incremental area under the ISR curve during the first 30 min during the OGTT (ΔISR0–30) was significantly decreased in IFG subjects (2.1 ± 0.3) compared with IGT (2.8 ± 0.2) and NGT (3.2 ± 0.2) (P < 0.001) subjects. The incremental area under the ISR curve divided by the incremental area under the plasma glucose concentration (ΔISR/ΔG0–30) was markedly decreased in IFG (0.19 ± 0.02) and IGT (0.15 ± 0.01) subjects compared with NGT (0.38 ± 0.06) (P < 0.01).

β-Cell glucose sensitivity, calculated with the Mari model, was significantly decreased (P < 0.01) in both IFG and IGT compared with NGT (Table 2 and Fig. 2A). β-Cell rate sensitivity was comparable in IGT and NGT, but was markedly decreased in IFG subjects (Table 2), and when related to the FPG in the entire group, it inversely related to the FPG (r = −0.34, P < 0.01). However, no significant correlation was observed between β-cell glucose sensitivity and 2-h plasma glucose concentration (r = 0.01, P = nonsignificant). The potentiation factor was significantly decreased in IGT compared with NGT, whereas it was significantly increased in IFG (Table 2). Although both IFG and IGT subjects had a decrease in β-cell glucose sensitivity, the time course of β-cell glucose sensitivity during the OGTT differed significantly between the two groups (Fig. 2B). In IGT subjects, β-cell glucose sensitivity was markedly decreased after 15 min and remained significantly lower than in NGT during the entire 120 min of the OGTT. β-Cell glucose sensitivity decreased in IGT during the first 60 min of the OGTT (0–60 min) was 0.19 ± 0.01 and 0.30 ± 0.02 in IGT and NGT, respectively (P < 0.001), and 0.14 ± 0.02 and 0.37 ± 0.04 during the second hour of the OGTT in IGT and NGT, respectively (P < 0.001). In contrast, β-cell glucose sensitivity in IFG subjects was markedly decreased during the first 60 min of the OGTT (0.17 ± 0.02, P < 0.001) but was markedly increased during the second hour of the OGTT (0.24 ± 0.02, P < 0.001) in IFG.

**TABLE 1**

Patient characteristics

|        | NGT | IGT | IFG | ANOVA |
|--------|-----|-----|-----|-------|
| n      | 78  | 48  | 46  |       |
| Age (years) | 37 ± 1 | 43 ± 2 | 46 ± 2 | <0.01 |
| BMI (kg/m²)  | 30.4 ± 0.8 | 32.9 ± 0.8 | 31.2 ± 0.9 | 0.08 |
| Sex (male)   | 23  | 13  | 25  | <0.05 |
| FPG (mg/dL)  | 91 ± 1 | 91 ± 1 | 106 ± 1 | <0.0001 |
| 2-h PG (mg/dL)  | 112 ± 2 | 161 ± 2 | 118 ± 2 | <0.0001 |

2-h PG, 2-h plasma glucose concentration; FPI, fasting plasma insulin concentration.
and 46

Insulin secretion at 5.5 mM × 10^2

Potentiation (fold) 1.4

Glucose sensitivity (pmol·min⁻¹·m⁻²·mM⁻¹)

TABLE 2

Model-derived \( β \)-cell parameters in NGT, IGT, and IFG subjects

| Parameter                                | NGT        | IGT        | IFG        | ANOVA     |
|------------------------------------------|------------|------------|------------|-----------|
| Glucose sensitivity \( \Delta \)          | 172 ± 14   | 101 ± 7*   | 111 ± 10*  | <0.001    |
| Rate sensitivity \( \Delta \)             | 1,512 ± 109| 1,673 ± 153| 863 ± 165* | <0.001    |
| Potentiation (fold)                       | 1.4 ± 0.1  | 1.1 ± 0.1# | 1.6 ± 0.1# | <0.01     |
| Insulin secretion at 5.5 mM \( \Delta \)   | 162 ± 15   | 159 ± 11   | 83 ± 7*    | <0.0001   |

*\( P < 0.001 \) compared with NGT. \#\( P < 0.05 \) compared with NGT.

progressively increased with time, reaching a value comparable to NGT subjects at 90 min. \( β \)-Cell glucose sensitivity during the second hour of the OGTT was 0.34 ± 0.06, \( P = \) nonsignificant compared with NGT.

The characteristics of subjects who received the hyperglycemic clamp (32 NGT, 14 IGT, 24 IFG; age 39 ± 2, 42 ± 2, and 46 ± 2 years, respectively, and BMI 29.9 ± 0.9, 32.6 ± 0.9, and 30.9 ± 1.0, respectively) were similar to the entire group.

During hyperglycemic clamp, IFG subjects had lower first-phase insulin secretion (measured as \( \Delta \)-C-peptide \( \text{[AUC]}\_0–12 \)) compared with NGT, whereas IGT subjects had a comparable \( \Delta \)-C-peptide \( \text{[AUC]}\_0–12 \) (Table 3). In contrast, subjects with IGT had a significant decrease in the second-phase insulin secretion (\( \Delta \)-C-peptide \( \text{[AUC]}\_15–120 \)) compared with NGT subjects (Table 3), whereas \( \Delta \)-C-peptide \( \text{[AUC]}\_15–120 \) was significantly increased in IFG subjects.

The glucose infusion rate divided by the mean plasma glucose concentration during the hyperglycemic clamp (0–120), an index of insulin sensitivity (26), was markedly reduced by 54% in subjects with IGT (\( P < 0.01 \)) and only modestly reduced in IFG subjects (Table 3). Thus, the insulin secretion/insulin resistance (disposition) index for first-phase (0–12 min) insulin secretion during the hyperglycemic clamp was markedly decreased in both IFG and IGT compared with NGT subjects (by 47 and 52%, respectively, \( P < 0.01 \)). However, second-phase (15–120 min) insulin secretion/insulin resistance index was markedly decreased only in IGT subjects (by 64%, \( P < 0.01 \)).

When all subjects were pooled into one group, the increase in FPG concentration was associated with opposite changes in the first- and second-phase insulin secretion during the hyperglycemic clamp. Whereas the incremental area under the plasma C-peptide concentration curve for the first-phase insulin secretion (\( \Delta \)-C-peptide \( \text{[AUC]}\_0–12 \)) precipitously decreased with the increase in FPG concentration, \( r = 0.36, P < 0.001 \) (Fig. 3A), \( \Delta \)-C-peptide \( \text{[AUC]}\_15–120 \) for second-phase insulin secretion progressively increased with the increase in FPG concentration \( r = 0.29, P < 0.05 \) (Fig. 3B). Similarly, the insulin secretion/insulin resistance index for both first- (0–12 min) and second- (15–120 min) phase was inversely related to the 2-h plasma glucose concentration \( (r = -0.37, P < 0.01 \) and \( r = -0.51, P < 0.0001 \), respectively). However, only the insulin secretion/insulin resistance index for first-phase insulin secretion inversely correlated with the FPG concentration \( (r = -0.41, P < 0.001) \), whereas insulin secretion/insulin resistance index for second-phase insulin secretion tended to be positively correlated with the FPG concentration \( (r = 0.14, P = \) nonsignificant).

We used linear regression analysis to evaluate predictors of the first- and second-phase insulin secretions during the hyperglycemic clamp. Only FPG, \( β \)-cell glucose sensitivity, \( β \)-cell rate sensitivity, and glucose infusion rate were significant predictors of insulin secretion during the hyperglycemic clamp. FPG concentration, \( β \)-cell glucose sensitivity, and GIR were significant predictors of first-phase (0–12 min) insulin secretion, and a regression model that includes these three parameters explained 50% of the variance in first-phase insulin secretion (Table 4). Of note, when \( β \)-cell glucose sensitivity derived with the Mari model was replaced with \( β \)-cell glucose sensitivity during the first hour of the OGTT (0–60 min), \( β \)-cell rate sensitivity was no longer a predictor of the first-phase insulin secretion measured with the hyperglycemic clamp (Table 4). FPG concentration, \( β \)-cell glucose sensitivity during the first hour of the OGTT (0–60 min), and the potentiation factor were significant predictors of second-phase insulin secretion (Table 4), and a regression model that included the three parameters explained 93% of the variability in second-phase insulin secretion.
To examine the contribution of first- and second-phase insulin secretion during the hyperglycemic clamp and whole body insulin sensitivity to the incremental area under the plasma glucose concentration curve during the OGTT, we constructed a linear regression model with the incremental area under the plasma glucose concentration curve as the dependent variable and first- and second-phase insulin secretion, and glucose concentration was correlated with the increase in second-phase insulin secretion strongly and inversely correlated with 2-h plasma glucose concentration.

These results demonstrate that the defects in β-cell function associated with the increase in the FPG concentration, i.e., in IFG subjects, are very distinct from those associated with the increase in 2-h plasma glucose concentration, i.e., in IGT subjects.

Both IFG and IGT manifest decreased β-cell glucose sensitivity to the oral glucose stimulus compared with

**TABLE 3**

Metabolic parameters in NGT, IGT, and IFG subjects during the hyperglycemic clamp

|                  | NGT     | IGT     | IFG     | ANOVA   |
|------------------|---------|---------|---------|---------|
| GIR              | 8.2 ± 0.6 | 5.9 ± 0.7 | 8.2 ± 0.6 | 0.02    |
| MPI              | 37 ± 5   | 50 ± 7  | 58 ± 10 | <0.05   |
| GIR/MPI          | 0.31 ± 0.04 | 0.14 ± 0.03 | 0.26 ± 0.05 | NS      |
| MPI/MPC-pep      | 4.2 ± 0.4 | 5.5 ± 0.6 | 6.5 ± 0.9 | <0.01   |
| Fasting plasma C-peptide | 2.0 ± 0.2 | 2.6 ± 0.4 | 2.9 ± 0.3 | 0.002   |
| ΔC-pep (AUC)0–12 | 35 ± 3   | 34 ± 6  | 25 ± 4  | <0.05   |
| ΔC-pep (AUC)15–120 | 309 ± 24 | 255 ± 38 | 389 ± 34 | 0.01    |
| ΔG (mg/dL)       | 127 ± 1  | 127 ± 2 | 125 ± 1 |         |
| ΔC-pep (AUC)/ΔG ÷ IR | 0–12 min | 9.1 ± 1.0 | 4.3 ± 1.0 | 4.8 ± 0.7 | <0.001  |
|                  | 15–120 min | 98 ± 15   | 35 ± 8  | 93 ± 17 | <0.01    |

IR, insulin resistance. MPC-pep, mean plasma C-peptide concentration during the hyperglycemic clamp.
FIG. 3. Relationship between incremental area under the plasma C-peptide curve during the first phase (0–12 min, left) and second phase (15–120 min, right) of the hyperglycemic clamp. Triangles represent NGT subjects, open circles represent IGT subjects, and closed circles represent IFG subjects.

NGT. Since β-cell glucose sensitivity represents the ability of the β-cell to respond to a hyperglycemic stimulus, this observation indicates a “blindness” of the β-cell to the glucose stimulus in IFG and IGT compared with NGT individuals. However, the time course of decreased β-cell glucose sensitivity differs between the two states. Whereas the impairment in β-cell glucose sensitivity persisted through the 2-h of the OGTT in IGT, the defect was transient in IFG subjects. The restoration of β-cell glucose sensitivity after 60 min and the increase in potentiation factor in IFG subjects explain the near-normal second-phase insulin secretion during the first hour (0–60 min) during the OGTT.

The results of the current study help to explain the shape of the plasma glucose concentration following glucose ingestion in IFG subjects. The decrease in the first-phase insulin secretion contributes to the excessive rise in plasma glucose concentration during the first hour of the OGTT (ΔG0–60) (Table 5), and normal insulin sensitivity and normal second-phase insulin secretion are important determinants of the return in plasma glucose concentration to baseline fasting level during the second hour of the OGTT (ΔG60–120) (Table 5). Because first-phase insulin secretion plays an important role in priming the liver and inhibiting endogenous glucose production during the

TABLE 4
Determinants of first- and second-phase insulin secretion during the hyperglycemic clamp

|                      | First phase | Second phase |
|----------------------|------------|--------------|
|                      | β          | P            | β          | P            |
| FPG                  | –0.41      | 0.001        | –0.24      | 0.05         |
| Glucose sens. 0–60 min| 0.43       | 0.0001       | 0.27       | 0.05         |
| Rate sensitivity     | 0.1        | NS           | 0.04       | NS           |
| Potentiation         | 0.05       | NS           | 0.46       | 0.002        |
| GIR                  | 0.20       | 0.05         | –0.18      | NS           |

The first- and second-phase insulin secretion were measured with ΔISR0–12 and ΔISR12–60, respectively, during the hyperglycemic clamp, and values were adjusted for age, sex, and BMI. Glucose sensitivity, β-cell glucose sensitivity during the first hour (0–60 min) during the OGTT.
OGTT or a meal (31), the impairment in early phase insulin secretion in subjects with IFG would be expected to result in less inhibition of endogenous glucose production, and this would contribute to the excessive rise in plasma glucose concentration during the first 60 min of the OGTT in IFG.

Despite the excessive early (0–60 min) rise in plasma glucose concentration during the OGTT (9,10,18) and the defects in β-cell glucose sensitivity and rate sensitivity, subjects with IFG return their 2-h plasma glucose concentration to the baseline fasting glucose level. This can be explained by 1) the time-related improvement in β-cell glucose sensitivity during the 60–120 min time period; 2) the increase in potentiation factor (Table 2); and 3) normal to near-normal muscle insulin sensitivity (9). In marked contrast, the plasma glucose concentration during the last hour (60–120 min) of the OGTT in IGT subjects fails to decline whatsoever because of 1) the failure of the β-cell glucose sensitivity to improve with time (Fig. 2); 2) the decrease in potentiation factor; and 3) severe resistance to the action of insulin, as manifested both by the reduced Matsuda index of insulin sensitivity and the reduced GIR/mean plasma insulin concentration during the hyperglycemic clamp. Thus, the markedly elevated 2-h plasma glucose concentration during the OGTT in IGT versus IFG individuals is explained by the greater severity of the two basic core defects, insulin resistance and β-cell dysfunction, that characterize type 2 diabetes.

Only Mexican Americans participated in the current study. Because previous studies have demonstrated that the contribution of β-cell dysfunction to the deterioration in glucose tolerance could be ethnic dependent (32), validation of the results of the current study in other ethnic groups will help generalize the results.

In summary, the results of the current study demonstrate that the increase in FGP concentration in IFG subjects is associated with β-cell defects, which are distinct from the defects associated with the increase in 2-h plasma glucose concentration in IGT subjects. It follows that interventions aimed to halting/reversing β-cell failure should be individualized to each state.

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C.J., D.W., and L.N. contributed to data generation. A.M. and M.K. performed the data analysis. R.A.D. reviewed the manuscript and contributed to discussion. M.A.A.-G. contributed to data generation and analysis and wrote the manuscript. M.A.A.-G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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2-h PG, 2-h plasma glucose concentration.

## TABLE 5

Determinants of the increment in plasma glucose concentration during the OGTT

|            | ΔG60–60 | ΔG60–120 | 2-h PG |
|------------|---------|----------|--------|
| β          | P       | β        | P      |        |
| First phase| −0.48   | 0.01     | −0.09  | NS     | 0.17   | NS     |
| Second phase| 0.05   | NS       | 0.32   | 0.04   | 0.25   | NS     |
| GIR        | −0.12   | NS       | 0.55   | <0.001 | −0.50  | 0.003  |
| R2         | 0.19    | 0.007    | 0.27   | 0.001  | 0.27   | 0.001  |
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