Impaired fasting glucose with or without impaired glucose tolerance: progressive or parallel states of prediabetes?

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Am J Physiol Endocrinol Metab 295: E428–E435, 2008. First published June 3, 2008; doi:10.1152/ajpendo.90354.2008.—Our objective was to determine whether defects underlying impaired fasting glucose (IFG) are maintained and additive when combined with impaired glucose tolerance (IGT) (representing a progressive form of prediabetes) or are distinct in IFG/IGT (reflecting a parallel form of prediabetes). Volunteers with IFG (n = 10), IFG/IGT (n = 14), or normal glucose tolerance (NGT; n = 15) were matched for demographics and anthropometry. Insulin secretion was assessed using the glucose step-up protocol and insulin action through the use of a 2-stage hyperinsulinemic euglycemic clamp with infusion of [6,6-3H]glucose. Modeling of insulin secretory parameters revealed similar basal (βb) but diminished dynamic (βd) components in both IFG and IFG/IGT (P = 0.05 vs. NGT for both). Basal glucose rate of appearance (Rb) was higher in IFG compared with NGT (P < 0.01) and also, surprisingly, with IFG/IGT (P < 0.04). Moreover, glucose Rb suppressed more during the low-dose insulin clamp in IFG (P < 0.01 vs. NGT, P = 0.08 vs. IFG/IGT). Insulin-stimulated glucose uptake [glucose rate of disappearance (Ra)] was similar in IFG, IFG/IGT, and NGT throughout the clamp. We conclude that nuances of β-cell dysfunction observed in IFG were also noted in IFG/IGT. A trend for additional insulin secretory defects was observed in IFG/IGT, possibly suggesting progression in β-cell failure in this group. In contrast, basal glucose Rb and its suppressability with insulin were higher in IFG, but not IFG/IGT, compared with NGT. Together, these data indicate that IFG/IGT may be a distinct prediabetic syndrome rather than progression from IFG.

Insulin resistance; isotopes; clamp

PREVALENCE OF TYPE 2 DIABETES increased an alarming 61% between 1990 and 2001 (31) and currently affects 21 million Americans (9). Perhaps even more concerning are the 54 million Americans with prediabetes, up to 70% of whom will develop diabetes in their lifetime (26, 28, 38, 43). Although numerous trials have been undertaken to prevent diabetes in people with prediabetes (8, 19, 26, 43), surprisingly little is known about the pathophysiological differences between the types of prediabetes.

Prediabetes is not a singular entity but rather a heterogeneous group of metabolic defects that precede type 2 diabetes (28). “Impaired fasting glucose” (IFG) was added to “impaired glucose tolerance” (IGT) in the American Diabetes Association’s definitions of prediabetes in 1997 (2), as repeated observations show little concordance between the two (28, 42). The vast majority of literature to date has used indexes of fasting glucose and insulin to differentiate IFG from IGT in terms of their basic physiological defects (i.e., insulin secretion vs. insulin resistance using homeostasis model assessment) (11, 21, 37). The use of such indexes in small physiological studies has sparked considerable debate because the conclusions are inconsistent with more robust methods (16).

A small number of investigations have been undertaken to delineate the underlying defects in IFG from those in IGT a priori (3, 6, 16, 29, 46). Together, the evidence supports elements of β-cell dysfunction and insulin resistance in IFG and IGT that are somewhat distinct from one another (32). Concurrence of IFG with IGT is a presumed obligatory convergence point from isolated IFG or IGT in the pathway to diabetes. Interestingly, however, when IFG and IGT are combined, the result is not the simple addition of defects seen when IFG and IGT occur in isolation (6, 46). Whether IFG/IGT represents a third pathway (in addition to isolated IFG and IGT) vs. a final common pathway to diabetes is not clear. Elucidating defects in IFG/IGT is clinically relevant because progression to diabetes is three times higher than in isolated IFG or IGT (26, 28). Therefore, the aim of the current investigation was to determine whether defects underlying IFG in humans are maintained and additive when combined with IGT (representing a progressive form of prediabetes) or are distinct in IFG/IGT (reflecting a parallel form of prediabetes). We hypothesized that the defects seen in IFG would be unique vs. combined IFG/IGT, providing evidence that IFG/IGT may be a discreet prediabetic state.

MATERIALS AND METHODS

Subjects

Thirty-nine men and women between the ages of 45 and 70 were studied. Subjects were placed into one of the three groups on the basis of two 2-h 75-g oral glucose tolerance tests (2-h OGTT) separated by 1 wk: a control group with normal glucose tolerance (NGT; n = 15); fasting glucose <100 mg/dl and 2-h OGTT <140 mg/dl), IFG (n = 10; fasting glucose 100–125 mg/dl and 2-h OGTT <140 mg/dl), or combined IFG/IGT (n = 14; fasting glucose 100–125 mg/dl and 2-h OGTT 140–200 mg/dl) (18). All subjects were deemed healthy by a medical history, physical examination, and screening blood tests. Subjects were excluded for <0.5 or >5.0 U/ml thyroid-stimulating hormone, >250 mg/dl fasting triglycerides, >1.5 mg/dl creatinine, elevated liver function tests (>2× normal), <38% hematocrit, or

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<3.0 \times 10^3$ white blood cells. Use of medications for lipid and/or glucose lowering also excluded enrollees. Women must not have used hormone replacement therapy in the past year. In addition, subjects were sedentary ($<1.5 \text{ h of planned physical activity/wk}$) and non-smokers, and women were postmenopausal (defined as the cessation of menses $>1 \text{ yr prior to enrollment or FSH }>30 \text{ mIU/ml}$). Body composition was estimated from dual-energy X-ray absorptiometry (0.03 mRem), as described previously (35). Approval for this study was obtained from the Colorado Multiple Institutional Review Board prior to its commencement. Informed, written consent for participation was obtained from the subjects before they entered the study. All research-related activity conformed to the principles outlined in the Declaration of Helsinki (updated 2004).

**Prestudy Diet Control**

Subjects were fed a control diet for 3 days prior to admission to the General Clinical Research Center for study. The control diet was isocaloric [calculated as $1.4 \times (372 + (23.9 \times \text{ fat-free mass})]$], using the fat-free mass (FFM) measured by dual-energy X-ray absorptiometry. The diet composition was standardized as $30\%$ fat (saturated, polyunsaturated, and monounsaturated fats in a 1:1:1 ratio), $15\%$ protein, and $55\%$ carbohydrate.

**Testing Protocol**

Subjects were asked to fast overnight ($\sim 12 \text{ h}$) and were admitted to the General Clinical Research Center at 0730 on the morning of each study day (glucose step-up protocol and insulin clamp protocol, separated by $\sim 2 \text{ wk}$). Upon admission, an intravenous catheter was placed in an antecubital vein for infusion of glucose, and sampling catheter was placed in a dorsal hand vein of the contralateral arm. For all blood samples, the heated hand technique was used to arterialize the blood (27). Background sampling began 30 min after sampling catheters had been placed.

**Glucose step-up protocol.** Baseline blood samples were drawn for determination of insulin, glucose, C-peptide, free fatty acids (FFA), glycerol, and lactate concentrations. Twenty percent dextrose was then infused in a sequential stepwise fashion at 2, 4, 6, 8, and $10 \text{ mg/kg} \cdot \text{min}^{-1}$ for 40 min each. Blood was drawn every 10 min throughout the 240-min protocol for the determination of glucose, insulin, and C-peptide concentrations.

**Insulin clamp protocol.** Baseline blood samples were drawn for determination of background isotope enrichment as well as hormone and substrate (insulin, glucose, C-peptide, FFA, glycerol, and lactate) concentrations. For the measurement of glucose turnover, a primed (3.5 mg/kg) constant (0.04 mg/kg·min$^{-1}$) infusion of $[6,6^{3}^{\text{H}}]$glucose was initiated and continued through the end of the clamp. Resting blood measurements for tracer, hormone, and substrate concentrations (see above) were made over the final 30 min of the 120-min infusion to allow for equilibration of the tracer in the glucose pool. Indirect calorimetry was performed before resting blood sampling was started with a respiratory canopy (Sensormedics 2900; Sensormedics, Yorba Linda, CA).

A two-stage hyperinsulinemic euglycemic clamp was then initiated and continued for the next 3 h using the method of DeFronzo et al. (13). Briefly, a primed continuous infusion of insulin was infused at 4 mU·m$^{-2}·$min$^{-1}$ for 1.5 h and then increased to 40 mU·m$^{-2}·$min$^{-1}$ for the final 1.5 h. A variable infusion of 20% dextrose was infused to maintain blood glucose at $\sim 90 \text{ mg/dl}$. Blood was sampled every 5 min to determine glucose concentration, and the dextrose infusion adjusted as necessary. The dextrose was “spiked” with $15 \text{ mg/ml} [6,6^{3}^{\text{H}}]$glucose to minimize changes in isotope enrichment. Blood samples were taken over the final 30 min of both stages of the clamp for measurement of glucose kinetics as well as hormone and substrate concentrations (see above). Immediately prior to bold sampling during each stage, measurement of respiratory gas exchange was made.

**Analytical Procedures**

**Models of C-peptide secretion and kinetics.** Blood measurements of glucose and C-peptide concentrations taken during the glucose step-up protocol were input into the minimal-model insulin secretion (39). The model assumes that whole body C-peptide kinetics is described by the two-compartment model, originally proposed by Eaton et al. (15), also incorporating age associated changes in C-peptide kinetics as measured by Jiang et al. (24). The model assumes that insulin secretion is made up of two components, a dynamic component and a static one. The dynamic component is likely to represent secretion of promptly releasable insulin and is proportional to the rate of increase of glucose concentration through a parameter, dynamic $\beta$-cell responsivity index ($\Phi_d$; dimensionless), that defines the response to a given increment in glucose. The static component is believed to represent the provision of new insulin into a releasable pool and is characterized by a static responsivity index ($\Phi_s$; min$^{-1}$) and by a delay time constant (min). The global $\beta$-cell response to glucose ($\Phi_g$; min$^{-1}$) is a composite of $\Phi_d$ and $\Phi_s$. Finally, basal sensitivity index ($\Phi_b$; min$^{-1}$) measures basal insulin secretion rate over basal glucose concentration.

Posthepatic insulin appearance was predicted using insulin and glucose measurements taken during the step-up protocol in conjunction with the above-mentioned models. Hepatic insulin extraction was then calculated as the difference between from pre- and posthepatic insulin secretion (23).

Parameters of the model were estimated with their precision by weighted nonlinear least squares using the SAAM II software (4).

**Circulating hormone and substrate concentrations.** All samples were stored at $\sim 80^\circ \text{C}$ until analysis. Radioimmunoassay was used to determine insulin (Linco Research, St. Louis, MO) and C-peptide (y-counter; Diagnostic Products, Los Angeles, CA) concentrations. Standard enzymatic assays were used to measure glucose (COBA-Mira Plus; Roche Diagnostics, Mannheim, Germany), lactate (Sigma Kit no. 826; Sigma, St. Louis, MO), glycerol (Boehringer Mannheim Diagnostics, Mannheim, Germany), and FFA (NEFA kit; Wako Chemicals).

**Whole body substrate oxidation.** Whole body substrate oxidation was measured using indirect calorimetry. Oxygen consumption and carbon dioxide production are used to calculate metabolic rate as well as the oxidation of carbohydrate and fat using standard equations (45).

**Gas chromatography-mass spectroscopy methods.** Glucose isotopic enrichment was measured with gas chromatography-mass spectrometry (gas chromatography model 6890 series II and mass spectrometry model 5973A; Hewlett-Packard), using standard methods as described previously (33).

**Calculations**

Rates of glucose appearance ($R_a$), disappearance ($R_d$), and metabolic clearance rate (MCR) before the clamp were calculated using a modified Steele equation, as described by Wolfe (47), for stable isotopes. Equations described by Finegood et al. (17) were used to account for the tracer in the “spiked” dextrose solution during the insulin clamp. Nonoxidative glucose disposal was calculated by subtracting carbohydrate oxidation from glucose $R_d$.

**Statistical Analysis**

Comparisons between groups with IFG, IFG/IGT, and NGT were made using a one-way ANOVA, with least significant difference post hoc analyses to determine which means differed (SPSS, Chicago, IL). Differences within groups during the insulin clamp were made using repeated-measures ANOVA. Due to close matching of the groups, data are presented unadjusted. $R_d$ are expressed as milligram per kilogram FFM per minute. All data are presented as means $\pm$ SE. Overall significance was set at $P \leq 0.05$. 

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RESULTS

Demographics

The IFG/IGT group was older than the IFG group ($P < 0.05$) and contained more people with a first-degree relative who had type 2 diabetes ($P < 0.05$ vs. IFG and NGT). Sex, body mass index, percent body fat, and waist-to-hip ratio were similar among the groups (Table 1). All subjects were sedentary, engaging in <90 min of planned physical activity/wk.

Parameters of Insulin Secretion and Clearance

Mathematical modeling of the data collected during the glucose step-up protocol allowed examination of insulin secretory dynamics in humans in vivo. Basal β-cell responsivity ($\Phi_\beta$) was similar between the groups, whereas the stimulatory effect of the rate of change in glucose on insulin secretion ($\Phi_g$) was diminished in both IFG and IFG/IGT ($P = 0.05$ for both vs. NGT; Fig. 1, A and B). A nonsignificant trend for lower static ($\Phi_s = 0.07$ vs. IFG and NGT) and global β-cell responsivity indexes ($\Phi_\gamma; P = 0.07$ vs. NGT and $P = 0.08$ vs. IFG) in IFG/IGT was noted (Fig. 1, C and D). Overall, there was a linear correlation between 2-h glucose concentration and $\Phi_\gamma$ ($r^2 = 0.35, P = 0.03$), $\Phi_s$ ($r^2 = 0.45, P = 0.004$), and $\Phi_g$ ($r^2 = 0.46, P = 0.003$) but no such relationship between fasting glucose concentration and any parameter of insulin secretion. Further examination of β-cell function via calculation of the disposition index ($\Phi_\gamma \times$ glucose $R_\text{g}$ during the high-dose clamp) did not reveal any additional differences (data not shown). No correlations were noted between any parameter of insulin secretion and insulin action. No significant differences between the groups, with respect to hepatic insulin extraction, were appreciated at baseline or during the glucose step-up protocol (data not shown). Circulating concentrations of glucose and insulin during the step-up protocol are depicted in Fig. 2, A and B.

Hormone and Substrate Concentrations at Baseline and During the Clamp

Baseline. Fasting glucose concentration was higher in subjects with IFG and IFG/IGT vs. NGT ($P < 0.05$ for both, but not different between IFG and IFG/IGT), and 2-h glucose concentration was higher in subjects with IFG/IGT vs. NGT and IFG ($P < 0.05$ for both, but not different between NGT and IFG) by study design. Baseline C-peptide concentration was higher in IFG ($P < 0.05$ vs. NGT), and lactate concentration was diminished in both IFG and IFG/IGT ($P < 0.05$ vs. NGT). No difference in insulin, glycerol, or FFA levels between the groups was noted (Table 2). Baseline C-peptide concentration was higher in subjects with IFG/IGT vs. NGT ($P = 0.05$ vs. IFG/IGT), and 2-h glucose concentration was noted.

Low-dose clamp. Glucose infusion rate (GIR) during the low-dose clamp was lower in the two groups with prediabetes compared with those with NGT ($P < 0.05$) but comparable to one another (Table 2). GIR appeared related to baseline fasting ($r^2 = -0.366, P = 0.02$), but not 2-h ($r^2 = -0.031, P = 0.85$), glucose concentration. Glucose concentrations remained higher in IFG and IFG/IGT during the low-dose insulin infusion ($P < 0.05$ vs. NGT for both). Neither FFA concentrations nor the percent suppression (10–24%) were different between the groups. Insulin, C-peptide, lactate, and glycerol values were also not different during the low-dose clamp.

High-dose clamp. GIR during the high-dose clamp was not different between the groups (Table 2). Circulating concentrations of glucose, insulin, C-peptide, FFA, glycerol, and lactate, as well as percent suppression of FFA (82–90%) by insulin, were all similar between the groups.

Glucose Oxidation and Kinetics

Baseline. Respiratory exchange ratio (RER) was higher in IFG vs. NGT and IFG/IGT ($P < 0.05$ for both; Table 3). Consistent with the higher RER in IFG, carbohydrate (CHO) oxidation was higher and nonoxidative glucose disposal (NOGD) lower ($P < 0.05$ vs. NGT and IFG/IGT for all). Glucose $R_\text{g}$ (Fig. 3) was higher in IFG at baseline ($P = 0.003$ vs. NGT and $P = 0.03$ vs. IFG/IGT), with no difference noted in baseline $R_\text{g}$ normalized to FFM (Table 3). No difference between glucose $R_a$ and $R_d$ was observed between NGT and IFG/IGT. The MCR of glucose (Table 3) was similar between the groups at baseline. Baseline glucose $R_a$ was strongly correlated to fasting glucose concentration ($r^2 = 0.460, P = 0.004$) but not to 2-h glucose ($r^2 = -0.105, P = 0.53$).

Low-dose clamp. CHO oxidation was lower and NOGD higher, reflecting the lower RER, in IFG/IGT during the low-dose (4 mU·m²·min⁻¹) insulin infusion ($P < 0.05$ vs. IFG for all; Table 3). Glucose $R_a$ and $R_d$, as well as MCR, were comparable among all groups. Suppression of glucose $R_a$ was greatest in IFG (57%, $P = 0.008$ vs. 31% in NGT and $P = 0.08$ vs. 41% in IFG/IGT; Fig. 4). Glucose $R_d$ fell similarly in all groups during the low-dose insulin infusion, largely due to a decrease in glucose $R_a$. A nonsignificant trend toward suppression of glucose $R_d$ during the low-dose clamp and fasting ($r^2 = 0.311, P = 0.057$), but not 2-h ($r^2 = -0.032, P = 0.85$), glucose concentration was noted.

High-dose clamp. Glucose $R_a$ was completely and similarly suppressed in all groups during the high-dose (40 mU·m²·min⁻¹) insulin clamp (Fig. 4). Insulin-stimulated glucose uptake significantly, but similarly, increased in all groups during the high-dose clamp. No differences in glucose $R_a$, $R_d$, MCR, CHO oxidation, NOGD, or RER were observed (Table 3). Suppression of glucose $R_a$ during the high-dose clamp was related neither to fasting ($r^2 = -0.080, P = 0.64$) nor to 2-h ($r^2 = 0.066, P = 0.70$) glucose concentrations.

Table 1. Subject demographics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Sex (M/F)</th>
<th>Age, yr</th>
<th>Nonwhite Ethnicity (o)</th>
<th>FDR T2DM (o)</th>
<th>BMI, kg/m²</th>
<th>%Body Fat</th>
<th>W/H, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT</td>
<td>15</td>
<td>7/8</td>
<td>58±1.6</td>
<td>2</td>
<td>9</td>
<td>31±1.2</td>
<td>37±1.2</td>
<td>0.92±0.03</td>
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<tr>
<td>IFG</td>
<td>10</td>
<td>5/5</td>
<td>55±1.9</td>
<td>1</td>
<td>6‡</td>
<td>31±1.3</td>
<td>36±2.9</td>
<td>0.88±0.04</td>
</tr>
<tr>
<td>IFG/IGT</td>
<td>14</td>
<td>6/8</td>
<td>61±1.2†</td>
<td>3</td>
<td>11*</td>
<td>30±1.1</td>
<td>36±2.3</td>
<td>0.92±0.03</td>
</tr>
</tbody>
</table>

Values are means ± SE. NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; M, males; F, females; FDR T2DM, first-degree relatives with type 2 diabetes; BMI, body mass index; W/H, waist-to-hip ratio. All subjects engaged in <90 min of planned physical activity/wk. *P < 0.05 vs. NGT; †P < 0.05 vs. IFG; ‡P < 0.05 vs. IFG/IGT.
DISCUSSION

Unraveling the complexities of prediabetes is absolutely essential in expanding the current knowledge and armamentarium for preventing type 2 diabetes. Although two-thirds of people with diabetes are overweight or obese (1), only 2–13% of those who are simply obese will ever acquire diabetes (22), whereas ≈70% of those with prediabetes will acquire the disease (12, 26, 43). Therefore, understanding and exploiting differences between simple obesity and the different types of prediabetes has enormous public health implications. The current study was undertaken to determine whether defects underlying IFG are maintained and additive when combined with IGT (representing a progressive form of prediabetes) or are distinct in IFG/IGT (reflecting a parallel form of prediabetes). Nuances of β-cell dysfunction observed in IFG were also noted in IFG/IGT. A trend for additional insulin secretory defects was observed in IFG/IGT, suggesting progression in β-cell failure in this group. In contrast, basal glucose $R_{b}$ and its suppressability with insulin were higher in IFG, but not IFG/IGT, compared with NGT. Together, these data indicate that

Fig. 1. A: basal insulin secretion rate over basal glucose concentration [basal sensitivity index ($\Phi_b$)] in normal glucose tolerance (NGT), impaired fasting glucose (IFG), and IFG/impaired glucose tolerance (IGT) during the glucose step-up procedure. Values are means ± SE. B: the stimulatory effect of the rate of change in glucose on insulin secretion [dynamic β-cell responsivity index ($\Phi_d$)] in NGT, IFG, and IFG/IGT during the glucose step-up procedure. Values are means ± SE. *$P = 0.05$ vs. NGT. C: the stimulatory effect of glucose on insulin secretion at a steady-state level above basal [static responsivity index ($\Phi_s$)] in NGT, IFG, and IFG/IGT during the glucose step-up procedure. Values are means ± SE. $P = 0.07$, NGT vs. IFG/IGT. D: the global effect of glucose on insulin secretion [global β-cell response to glucose ($\Phi_g$) = $\Phi_b \times \Phi_d$] in NGT, IFG, and IFG/IGT during the glucose step-up procedure. Values are means ± SE. $P = 0.07$, NGT vs. IFG/IGT.
Hormone and substrate concentrations at baseline and during the clamp

Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Fasting Glucose, mg/dl</th>
<th>2-h Glucose, mg/dl</th>
<th>Insulin, μU/ml</th>
<th>C-Peptide, ng/ml</th>
<th>FFA, μmol/l</th>
<th>Glyceral, μmol/l</th>
<th>Lactate, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGT</td>
<td>91±1.2</td>
<td>102±6.7</td>
<td>10.0±1.8</td>
<td>2.6±0.2</td>
<td>585±37</td>
<td>88±9</td>
<td>0.7±0.09</td>
</tr>
<tr>
<td></td>
<td>IFG</td>
<td>112±3.0*</td>
<td>93±6.2</td>
<td>11.4±1.3</td>
<td>3.2±0.2*</td>
<td>543±43</td>
<td>101±19</td>
<td>0.5±0.07</td>
</tr>
<tr>
<td></td>
<td>IGT/IFG</td>
<td>111±2.4*</td>
<td>163±4.0</td>
<td>10.0±1.6</td>
<td>2.8±0.2</td>
<td>668±58</td>
<td>105±13</td>
<td>0.9±0.15†</td>
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</table>

Low-dose (4 mU·m²·min⁻¹) clamp

|                | NGT      | 93±1.0                 | 11.1±1.8         | 2.2±0.2      | 498±40         | 71±6        | 0.4±0.04      |
|                 | IFG      | 102±2.0*               | 12.6±0.7         | 2.6±0.2      | 491±50         | 82±10       | 0.5±0.07      |
|                 | IGT/IFG  | 102±1.6*               | 12.5±1.5         | 2.3±0.2      | 496±45         | 85±9        | 0.6±0.08      |

High-dose (40 mU·m²·min⁻¹) clamp

|                | NGT      | 89±1.0                 | 76±8             | 1.3±0.2      | 59±18          | 39±6        | 0.7±0.05      |
|                 | IFG      | 90±1.3                 | 70±10            | 1.3±0.2      | 97±41          | 45±8        | 0.6±0.07      |
|                 | IGT/IFG  | 89±2.7                 | 69±5.4           | 1.1±0.1      | 65±19          | 56±14       | 0.8±0.10      |

Values are means ± SE. GIR, glucose infusion rate. *P < 0.05 vs. NGT; †P < 0.05 vs. IFG; ‡P < 0.05 vs. IFG/IGT.

Indeed, our study is in agreement with others where higher basal glucose Rₐ (a measure of EGP) in isolated IFG has been observed, but the difference is small (13%) and can either appear (6) or disappear (46) with adjustment of the data for confounding variables. Importantly, however, fasting glucose concentration correlated with basal glucose Rₐ, providing evidence that excess EGP plays an important role in IFG. Higher basal Rₐ in our study was associated with a higher RER, reflecting greater CHO oxidation in IFG. In contrast, nonoxidative glucose uptake, Rₐ, and MCR were not different in IFG vs. NGT. Thus, decreased peripheral insulin sensitivity, characteristic of type 2 diabetes, does not appear to be a major feature of isolated IFG in our study as it is in others (16, 29).

Why basal Rₐ is higher in IFG remains speculative. Hormonal and substrate mediators of EGP, such as insulin, lactate, glyceral, and FFA, were not different between IFG and NGT in the current study at baseline or at any other time point. Glucagon was not measured in this study but has been found to contribute more to EGP in IFG when IFG is combined with IGT or diabetes (6). To our knowledge, the role of cortisol or catecholamines in mediating EGP in IFG has not been studied. Consistent with the findings of Bock et al. (6), basal EGP is inappropriate given the fasting hyperglycemia in this group. An aspect of “glucose effectiveness” (40), the ability of glucose to regulate its own production, appears diminished. Others have observed fasting hyperinsulinemia in IFG, and thus higher EGP in this group may also be due, in part, to hepatic insulin resistance (5, 46). Taking our data with others, decreased glucose effectiveness and hepatic insulin resistance may be permissive for higher EGP in IFG.

Interestingly, our study did not observe fasting hyperinsulinemia in IFG but rather higher fasting C-peptide concentration. Disproportionate insulin-to-C-peptide ratio implicates a difference in whole body insulin clearance (7). Considerable data exist that insulin clearance normally decreases during the development of obesity (24, 44) and diabetes (25, 30) and is a presumed adaptation to preserve β-cell function. However, hepatic insulin extraction (by mathematical modeling) was not different in IFG vs. NGT. Dynamic insulin secretion (0ₘₐ; Fig. 1B), believed to represent the promptly releasable pool of stored insulin (1st phase), was impaired in IFG as in other IFG/IGT could be a distinct prediabetic syndrome rather than simply a progression from IFG.

**IFG**

By definition, people with isolated IFG have mild fasting hyperglycemia but achieve euglycemia 2 h after an OGTT. Why insulin secretion is able to overcome postprandial, but not fasting, hyperglycemia is not clear. Fasting glucose concentration is purportedly proportional to endogenous glucose production (EGP) in type 2 diabetes (14) and thus would be expected to be higher in people with IFG in the progression to diabetes.

Fig. 2. A: blood glucose concentration (mg/dl) during the 200-min glucose step-up protocol in NGT, IFG, and IGT. B: blood insulin concentration (μU/ml) during the 200-min glucose step-up protocol in NGT, IFG, and IGT/IGT.
fig. 3. Glucose rate of appearance (Ra; mg•kg⁻¹•min⁻¹) in NGT, IFG, IGT, and IGT/IFG during rest, low-dose insulin infusion (4 mU m²/min), and high-dose (40 mU m²/min) insulin infusion. Values are means ± SE. *P = 0.003 vs. NGT; †P = 0.03 vs. IFG/IGT.

Fig. 4. Suppression of glucose Ra (%) during the low-dose (40 mU•m²•min⁻¹) and high-dose (40 mU•m²•min⁻¹) insulin infusions. Values are means ± SE. *P = 0.08 vs. NGT.

Table 3. Glucose oxidation and kinetics

<table>
<thead>
<tr>
<th></th>
<th>RER</th>
<th>CHO Oxidation, mg•kg⁻¹•min⁻¹</th>
<th>NOGD, mg•kg⁻¹•min⁻¹</th>
<th>Rd, mg•kg•FFM⁻¹•min⁻¹</th>
<th>MCR, ml•kg⁻¹•min⁻¹</th>
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<td><strong>Baseline</strong></td>
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<td>NGT</td>
<td>0.77±0.01</td>
<td>0.44±0.13</td>
<td>1.28±0.11</td>
<td>1.70±0.04</td>
<td>1.92±0.06</td>
</tr>
<tr>
<td>IFG</td>
<td>0.82±0.02*</td>
<td>1.12±0.25*</td>
<td>0.82±0.24*</td>
<td>1.93±0.07*</td>
<td>1.95±0.10</td>
</tr>
<tr>
<td>IGT/IFG</td>
<td>0.76±0.02†</td>
<td>0.51±0.18†</td>
<td>1.23±0.20†</td>
<td>1.77±0.06</td>
<td>1.76±0.14</td>
</tr>
<tr>
<td><strong>Low-dose (4 mU•m²•min⁻¹) clamp</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>0.81±0.04</td>
<td>0.69±0.27</td>
<td>0.70±0.29</td>
<td>1.35±0.08</td>
<td>1.62±0.11</td>
</tr>
<tr>
<td>IFG</td>
<td>0.80±0.02</td>
<td>0.78±0.22</td>
<td>0.34±0.25</td>
<td>1.41±0.08</td>
<td>1.50±0.08</td>
</tr>
<tr>
<td>IGT/IFG</td>
<td>0.76±0.01</td>
<td>0.34±0.12†</td>
<td>1.12±0.17†</td>
<td>1.40±0.11</td>
<td>1.49±0.10</td>
</tr>
<tr>
<td><strong>High-dose (40 mU•m²•min⁻¹) clamp</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT</td>
<td>0.82±0.02</td>
<td>0.94±0.16</td>
<td>2.07±0.33</td>
<td>3.25±0.37</td>
<td>4.28±0.51</td>
</tr>
<tr>
<td>IFG</td>
<td>0.84±0.03</td>
<td>1.43±0.44</td>
<td>1.79±0.41</td>
<td>3.04±0.75</td>
<td>4.31±0.62</td>
</tr>
<tr>
<td>IGT/IFG</td>
<td>0.84±0.01</td>
<td>1.30±0.14</td>
<td>1.37±0.29</td>
<td>2.53±0.31</td>
<td>3.08±0.37</td>
</tr>
</tbody>
</table>

Values are means ± SE. RER, respiratory exchange ratio; CHO, carbohydrate; NOGD, nonoxidative glucose disposal; Rd, glucose rate of disappearance; MCR, metabolic clearance rate of glucose. *P < 0.05 vs. NGT; †P < 0.05 vs. IFG.
however, basal glucose $R_a$ was likely inappropriate given fasting hyperglycemia in IGT/IFG, suggesting a mild decrease in hepatic glucose effectiveness in this group (6). Although noteworthy, diminished glucose effectiveness in both IFG and IFG/IGT is limited to the fasted state, as evidenced by greater suppression of glucose $R_a$ in IFG and greater NOGD in IFG/IGT during the low-dose insulin infusion. Importantly, the low-dose insulin infusion decreased circulating glucose concentration, but did not change circulating insulin, in IFG and IFG/IGT. This observation supports the contention that diminished hepatic glucose effectiveness, rather than hepatic insulin resistance, may be as much, or more, contributory to increased glucose $R_a$ in groups with IFG. Our study is consistent with some (5, 46), but not all (3), in this regard. More surprising was the lack of notable decrement in peripheral insulin action in either IFG or IFG/IGT vs. NGT in the current study and may relate to the close anthropometric matching between groups. Previous work has implicated obesity (10, 20), rather than glucose dysregulation (36, 46), in the decline of peripheral insulin action characteristic of diabetes. Alternatively, small numbers in the groups may have obscured differences, as Tripathy et al. (41) noted 19% lower peripheral insulin sensitivity comparing overweight people with IFG/IGT ($n = 29$) to those with NGT ($n = 216$). In summary, subtle impairment in hepatic glucose effectiveness coupled with no decrement noted in peripheral glucose uptake in the current study highlights the likely importance of global $\beta$-cell failure in the pathway from IFG/IGT to diabetes.

Whether the greater age, higher prevalence of first-degree relatives with type 2 diabetes, and/or higher baseline lactate concentration among those with IFG/IGT vs. IFG had additional unmeasured effects is unknown. However, lower insulin action observed with aging (23) or in first-degree relatives of those with type 2 diabetes (34) would have increased the likelihood of finding differences between groups; thus the lack of such a difference strengthens the conclusions. Close anthropometric matching between groups implies a central role for obesity, rather than glucose dysregulation, as dictating peripheral insulin action. Indeed, previous work has noted far greater differences in peripheral insulin action when obese NGT vs. lean NGT is compared (10, 20) than when obese NGT vs. prediabetes is compared (36, 46). In summary, no differences were noted in peripheral insulin action between IFG, IFG/IGT, and NGT in the current study. Somewhat greater $\beta$-cell dysfunction without the excess EGP seen in IFG suggests IFG/IGT as a parallel, rather than progressive, form of prediabetes.

Although subjects included in this analysis were well matched, there are several limitations in the current study worth noting. To focus on aspects of glucose dysregulation, and not obesity per se, subjects were matched for body mass index, percent body fat, and waist-to-hip ratio, and no lean control group was studied. Furthermore, the NGT group may not have been a true control due to the high prevalence of first-degree relatives with type 2 diabetes, a group known to have altered metabolism (34). Therefore, differences in insulin action and secretion were likely underestimated compared with “normal.” In addition, no group with isolated IGT was included. Several borderline significant trends and small absolute differences were noted, likely due to a small sample size. Small sample size increases the possibility that type II statistical errors will arise in data analysis. Despite this limitation, similar effect sizes in other studies with larger sample sizes have been observed (6, 46). Furthermore, the calculated probability that the lack of difference in basal glucose $R_a$ between NGT and IFG/IGT was due to a type II statistical error was <5%. Together, this suggests that the differences between the types of prediabetes are subtle. Deficits in insulin secretion are more easily observed, whereas impairments in insulin action are limited largely to the fasted state.

In conclusion, nuances of $\beta$-cell dysfunction observed in IFG were also noted in IFG/IGT. A nonsignificant trend for additional insulin secretory defects was observed in IFG/IGT, suggesting progression in $\beta$-cell failure in this group. In contrast, basal glucose $R_a$ and its suppressability with insulin were higher in IFG, but not IFG/IGT, compared with NGT. Absolute differences between groups were small but important because they have implications for specific treatment or prevention strategies. Together, these data indicate that IFG/IGT may be a distinct prediabetic syndrome rather than a progression from IFG.

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GRANTS

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