Metabolic Characteristics of Individuals With Impaired Fasting Glucose and/or Impaired Glucose Tolerance

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With the release of the new 1997 American Diabetes Association diagnostic criteria, a new category was introduced, termed "impaired fasting glucose" (IFG). The metabolic abnormalities of individuals with IFG, compared with those with impaired glucose tolerance (IGT) (World Health Organization criteria), remain to be elucidated. We assessed insulin action (hyperinsulinemic clamp), insulin secretion (25-g intravenous glucose tolerance test), and endogenous glucose output (EGO) (3-^{3}H-glucose) in 434 nondiabetic Pima Indians with either normal (NFG; <6.1 mmol/l) or impaired (IFG; 6.1–7.0 mmol/l) fasting glucose and with either normal (NGT; 2-h glucose <7.8 mmol/l) or impaired (IGT; 2-h glucose 7.8–11.1 mmol/l) glucose tolerance: NFG/NGT (n = 307), IFG/NGT (n = 11), NFG/IGT (n = 98), and IFG/IGT (n = 18). Compared with the NFG/NGT group, individuals with IFG/NGT had lower maximal insulin-stimulated glucose disposal (M; –20%, P < 0.01), a lower acute insulin response (AIR) to intravenous glucose (–33%, P < 0.05), and higher EGO (8%, P = 0.055). Individuals with NFG/IGT also had lower M (–21%, P < 0.001) and lower AIR (–8%, P < 0.05), but normal EGO (–1%, NS). Individuals with IFG/IGT showed the most severe abnormalities in M (–27%), AIR (–51%), and EGO (+13%) (all P < 0.001 compared with NFG/NGT). These group differences could be explained by the observation that AIR and EGO, but not M, were more strongly related to the fasting than to the 2-h glucose concentration. Thus, Pima Indians with isolated IFG and isolated IGT show similar impairments in insulin action, but those with isolated IFG have a more pronounced defect in early insulin secretion and, in addition, increased EGO. More severe metabolic abnormalities are present in Pima Indians with combined IFG and IGT. *Diabetes* 48:2197–2203, 1999

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ADA, American Diabetes Association; AIR, acute insulin response; EGO, endogenous glucose output; EMBS, estimated metabolic body size; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; M, insulin-stimulated glucose disposal; NFG, normal fasting glucose; NGT, normal glucose tolerance; WHO, World Health Organization.

Glucose tolerance is traditionally classified by the 1985 World Health Organization (WHO) criteria (1) into three categories: normal (NGT), impaired (IGT), and diabetic. The category of IGT, defined by an impaired glucose response 2 h after an oral glucose load (7.8–11.1 mmol/l) but a "normal" fasting plasma glucose concentration (<7.8 mmol/l) (1), represents a metabolic state intermediate between normal and diabetic glucose homeostasis. Numerous cross-sectional studies have examined the metabolic characteristics of individuals with IGT and have shown that they are, on average, more obese and more insulin resistant than individuals with NGT, and are typically hyperinsulinemic (2–7). Whether insulin secretion is impaired in individuals with IGT remains controversial because both lower and normal early and late insulin secretory responses have been reported (2,4,6–11). Basal endogenous glucose output (EGO) was not found to be increased in individuals with IGT and is thus typically considered a later abnormality that only occurs with the onset type 2 diabetes (2,12–14).

In 1997, the American Diabetes Association (ADA) released new diagnostic recommendations promoting the use of fasting rather than 2-h glucose concentrations for screening and diagnosis of diabetes. In addition to lowering the fasting plasma glucose level diagnostic of diabetes from 7.8 to 7.0 mmol/l, a new category was introduced, termed "impaired fasting glucose" (IFG) (fasting plasma glucose concentration 6.1–7.0 mmol/l) (15). Analogous to the WHO category of IGT, this new diagnostic entity is meant to be an intermediate metabolic state between normal and diabetic glucose homeostasis (1,15). The choice of 6.1 mmol/l as the lower cutoff level for IFG was based in large part on epidemiological data on the risk of micro- and macrovascular complications (15–19), but is also supported by pathophysiological data because it is near the level above which early phase insulin secretion is lost (15,20).

When both the 1985 WHO and the 1997 ADA diagnostic criteria are applied, it is possible to classify impaired glucose homeostasis into three different subcategories: *1*) isolated IFG (impaired fasting but normal 2-h glucose), *2*) isolated IGT (normal fasting but impaired 2-h glucose), and *3*) combined IFG and IGT (impaired fasting and 2-h glucose). The metabolic abnormalities underlying these different groups of impaired glucose homeostasis remain to be elucidated. In particular, it is unknown whether the metabolic characteristics of individuals with isolated IFG are comparable with

those of individuals with isolated IGT, and whether more severe abnormalities are present when both the fasting and the 2-h glucose concentrations are impaired. The first aim of the present study, therefore, was to examine the metabolic characteristics of these three different groups of impaired glucose homeostasis in Pima Indians of Arizona, a population with a high prevalence of glucose intolerance and type 2 diabetes (21).

Categorization of glucose homeostasis by both ADA and WHO criteria is based on arbitrary cutoff points on the continuous scales of fasting and 2-h glucose concentration. However, insulin action, insulin secretion, and EGO may be related differently to fasting and the 2-h glucose concentrations (22). The second aim of our study, therefore, was to further elucidate, within the nondiabetic range, the relationship of insulin action, insulin secretion, and EGO to glycemia using continua of fasting and 2-h glucose concentrations rather than clinical categories.

RESEARCH DESIGN AND METHODS

Subjects. The subjects in this analysis were all Native Americans from the Gila River Indian Community and were all nondiabetic according to both the 1997 ADA (15) and the 1985 WHO (1) diagnostic criteria (fasting and 2-h plasma glucose concentrations <7.0 and <11.1 mmol/l, respectively). They were participants in an ongoing study of the metabolic determinants of type 2 diabetes (23), and were all healthy according to a physical examination and routine laboratory tests. None of the subjects took medication known to affect glucose or insulin metabolism for at least 1 month before the study. Of the 434 nondiabetic subjects enrolled in the study (Table 1), 405 were classified as having normal fasting glucose (NFG) (fasting plasma glucose concentration <6.1 mmol/l) and 29 as having IFG (6.1–7.0 mmol/l), according to the 1997 ADA criteria (15). Of the 405 subjects with NFG, 307 had normal glucose tolerance (NGT) (2-h plasma glucose concentration <7.8 mmol/l) (NFG/NGT group) and 98 had impaired glucose tolerance (IGT) (7.8–11.1 mmol/l) (NFG/IGT group), according to the 1985 WHO criteria (1). Of the 29 subjects with IFG, 11 had NGT (IFG/NGT group) and 18 had IGT (IFG/IGT group) (Table 1). After giving written informed consent, subjects were admitted to the National Institutes of Health Clinical Research Unit in Phoenix, AZ, where they were fed a weight-maintaining diet (50% of calories from carbohydrate, 30% from fat, and 20% from protein) and abstained from strenuous exercise. After at least 3 days on the diet, a series of tests was conducted to assess body composition and body fat distribution, glucose tolerance, insulin action, insulin secretion, and EGO. The study protocol was approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and by the Tribal Council of the Gila River Indian Community.

Anthropometric measurements. Body composition was estimated by underwater weighing with simultaneous determination of residual lung volume by helium dilution (24) or by total body dual energy X-ray absorptiometry (DPX-L; Lunar Radiation, Madison, WI) (25). Percent body fat, fat mass, and fat-free mass were calculated as described (26). Measurements using the two different methods were made comparable using a previously derived conversion equation (27). Waist and thigh circumferences were measured at the umbilicus and the gluteal fold in the supine and standing position, respectively, and the waist-to-thigh ratio was calculated as an index of body fat distribution (28).

Oral glucose tolerance test. After a 12-h overnight fast, subjects underwent a 75-g oral glucose tolerance test (1). Two venous blood samples were drawn at baseline and one after 120 min for determination of plasma glucose and insulin concentrations. Fasting plasma glucose and insulin concentrations were calculated as the average of the two baseline samples. Based on the fasting and 2-h plasma glucose concentration, subjects were categorized as having either NFG or IFG and as having either NGT or IGT as described above. In all individuals categorized as IFG, the diagnosis was confirmed on a separate day.

Two-step hyperinsulinemic-euglycemic glucose clamp. Insulin action was assessed at physiologic and supraphysiologic insulin concentrations during a two-step hyperinsulinemic-euglycemic glucose clamp as described (23,29). In brief, after an overnight fast, a primed continuous intravenous insulin infusion was administered for 100 min at a constant rate of 40 mU · m^{-2} body surface area · min^{-1} (low dose), followed by a second 100-min infusion at a rate of 400 mU · m^{-2} · min^{-1} (high dose). These infusions achieved steady-state plasma insulin concentrations of 918 ± 234 pmol/l and 13,524 ± 4,272 pmol/l (mean ± SD), respectively. The insulin concentrations achieved during the clamp did not differ among the four groups. Plasma glucose concentrations were maintained at ~5.0 mmol/l, with a variable infusion of a 20% glucose solution. The rate of total insulin-stimulated glucose disposal (*M*) was calculated for the last 40 min of the low-dose (*M*-low) and high-dose (*M*-high) insulin infusion as described (23,29). Indirect calorimetry measurements using a ventilated hood system (30) were performed throughout the clamp to assess the rates of oxidative and nonoxidative glucose disposal. EGO was determined at baseline and during the low dose insulin infusion using a primed (30 µCi) continuous (0.3 µCi/min) 3-^{3}H-glucose infusion (23,29). Suppression of EGO at the end of the low-dose insulin infusion was calculated as percent change from baseline. All measurements derived from the glucose clamp were normalized to the estimated metabolic body size (EMBS = fat-free mass + 17.7 kg) (31).

Intravenous glucose tolerance test. Insulin secretion was measured in response to a 25-g intravenous glucose bolus injected over 3 min (32). The acute insulin response (AIR) to intravenous glucose was calculated as the average incremental plasma insulin concentration from the 3rd to the 5th min after the glucose bolus (32).

Analytic procedures. Plasma glucose concentrations were determined by the glucose oxidase method (Beckman Instruments, Fullerton, CA) and plasma insulin concentration by the Herbert modification (33) of the method of Yalow and Berson (34) or by an automated radioimmunoassay (Concept 4; ICN, Costa Mesa, CA).

Statistical analysis. Statistical analyses were performed using software from the SAS Institute, Cary, NC (35). Log-transformed values of AIR and *M*-low were used for the statistical tests to obtain a normal distribution of these measures. Results are given as means ± SD in the text and tables and as means ± SE in Fig. 1.

Metabolic characteristics were compared among the four groups with different glucose homeostasis using general linear regression models. Group comparisons were made with and without adjustment for age, sex, and percent body fat. AIR was additionally adjusted for *M*-low. In a further analysis, the individual results for *M*-low, *M*-high, AIR, and EGO of the 434 subjects were plotted against the fasting and 2-h glucose concentrations. General linear regression models were used to determine the relation of *M*-low, *M*-high, AIR, and EGO to the fasting and 2-h glucose concentrations.

RESULTS

Physical characteristics. The physical characteristics of the four groups are given in Table 1. The relative proportion of female subjects and the mean age were lower in the

TABLE 1
Physical characteristics of the study population

	NFG/NGT	IFG/NGT	NFG/IGT	IFG/IGT
n (F/M)	307 (103/204)	11 (9/2)	98 (50/48)	18 (14/4)
Age (years)	26 ± 6*	30 ± 6†	29 ± 6†	30 ± 7†
Body weight (kg)	91.0 ± 22.7*	113.6 ± 18.2†	96.8 ± 22.3‡	110.7 ± 20.3†
Body fat (%)	31 ± 9*	41 ± 4†	35±7‡	41 ± 6†
Fat mass (kg)	28.9 ± 13.1*	47.5 ± 10.0†	34.5 ± 11.7‡	46.2 ± 12.9†
Fat-free mass (kg)	62.1 ± 12.9*	66.1 ± 10.2†	62.3 ± 13.9‡	64.5 ± 10.8†
Waist-to-thigh ratio	1.62 ± 0.15*	1.72 ± 0.17†,‡	1.67 ± 0.15†	1.79 ± 0.16‡

Data are means ± SD. Anthropometric comparisons are adjusted for age and sex. Values not sharing a common symbol are significantly different ($P < 0.05$).

NFG/NGT group compared with the three groups with impaired glucose homeostasis. After adjustment for age and sex, individuals with IFG/NGT, NFG/IGT, and IFG/IGT all had higher body weight, percent body fat, fat mass, fat-free mass, and waist-to-thigh ratio than those with NFG/NGT. Among the three groups with impaired glucose homeostasis, body weight, percent body fat, fat mass, and fat-free mass were lower in individuals with NFG/IGT compared with those with IFG/NGT and IFG/IGT (Table 1).

Oral glucose tolerance test. The results of the oral glucose tolerance test are given in Table 2. By design, the fasting plasma glucose concentration was higher in the two groups with IFG than in the two groups with NFG. The fasting plasma glucose concentration was not different between the two groups with IFG, but was higher in the NFG/IGT group compared with the NFG/NGT group. Also by design, the 2-h plasma glucose concentration was higher in the two groups with IGT than in the two groups with NGT. The 2-h plasma glucose concentration was not different between the two groups with IGT, but was higher in the IFG/NGT group than in the NFG/NGT group (Table 2).

The fasting plasma insulin concentration was higher in the IFG/NGT, NFG/IGT, and IFG/IGT groups than in the NFG/NGT group (Table 2). Among the three groups with impaired glucose homeostasis, the fasting plasma insulin concentration was higher in the IFG/NGT and IFG/IGT groups than in the NFG/IGT group, but these differences were not significant after adjustment for age, sex, and percent body fat. The 2-h plasma insulin concentration was higher in the IFG/NGT, NFG/IGT, and IFG/IGT groups than in the NFG/NGT group (Table 2). Among the three groups with impaired glucose homeostasis, there were no differences in the 2-h plasma insulin concentration, but when adjusted for age, sex, and percent body fat, the 2-h plasma insulin concentration was higher in the NFG/IGT group than in the IFG/NGT group (Table 2).

Insulin-stimulated glucose disposal. Insulin-stimulated glucose disposal at the low-dose insulin infusion (*M*-low) was 29% lower in the IFG/NGT group, 27% lower in the NFG/IGT group, and 32% lower in the IFG/IGT group, compared with the NFG/NGT group (all $P < 0.001$) (Fig. 1*A*). There were no differences in *M*-low between the three groups with impaired glucose homeostasis. After adjustment for age, sex, and percent body fat, the decrease in *M*-low remained significant in the NFG/IGT and IFG/IGT groups, but not in the IFG/NGT group. The lower *M*-low in all three groups with impaired glucose homeostasis was mainly due to a lower rate of nonoxidative glucose disposal, whereas oxidative glucose disposal did not differ among the four groups (Fig. 1*A*).

Insulin-stimulated glucose disposal at the high-dose insulin infusion (*M*-high) was 20% lower in the IFG/NGT group ($P < 0.01$), 21% lower in the NFG/IGT group, and 27% lower in the IFG/IGT group (both $P < 0.001$), compared with the NFG/NGT group (Fig. 1*B*). There were no differences in *M*-high between the three groups with impaired glucose homeostasis. *M*-high remained decreased in all three groups after adjustment for age, sex, and percent body fat. As with *M*-low, the lower *M*-high in the IFG/NGT, NFG/IGT, and IFG/IGT groups was mainly due to a lower rate of nonoxidative glucose disposal, whereas oxidative glucose disposal was not different from the NFG/NGT group (Fig. 1*B*).

There was a negative linear relationship between *M*-low and both the fasting and the 2-h plasma glucose concentrations ($r = –0.35$ and $–0.43$, respectively, both $P < 0.0001$) (Fig. 2*A*). *M*-high was also linearly related to the fasting plasma glucose concentration ($r = –0.28$, $P < 0.0001$), whereas the relationship between *M*-high and the 2-h plasma glucose concentration was curvilinear ($r = –0.45$, $P < 0.0001$) (Fig. 2*B*). Both fasting and 2-h plasma glucose concentrations were significantly and independently related to *M*-low and *M*-high in multiple regression analyses.

AIR. Compared with the NFG/NGT group, the AIR was 33% lower in the IFG/NGT group and 8% lower in the NFG/IGT group (both $P < 0.05$), with no significant difference between the IFG/NGT and NFG/IGT group (Fig. 1*C*). AIR was 51% lower in the IFG/IGT group than in the NFG/NGT group ($P < 0.001$), and was also lower compared with the NFG/IGT group (–46%, $P < 0.001$), but not compared with the IFG/NGT group (–26%, NS). The statistical results remained the same after adjustment for age, sex, and percent body fat, in addition to *M*-low.

AIR was negatively correlated with both the fasting ($r = –0.35$, $P < 0.0001$) and the 2-h ($r = –0.17$, $P < 0.001$) plasma glucose concentration (Fig. 2*C*). The relationship was curvilinear for the fasting but linear for the 2-h plasma glucose concentration (Fig. 2*C*). In a multiple regression analysis, AIR was only related to the fasting plasma glucose concentration ($P < 0.0001$), with no additional independent relation to the 2-h plasma glucose concentration.

EGO. EGO was 8% higher in the IFG/NGT group ($P = 0.055$) and 13% higher in the IFG/IGT group ($P < 0.0001$) compared with the NFG/NGT group (Fig. 1*D*). In contrast, EGO in the NFG/IGT group was not different from that in the NFG/NGT group (–1%, NS). Among the three groups with impaired glu-

TABLE 2
Results of the oral glucose tolerance test

	NFG/NGT	IFG/NGT	NFG/IGT	IFG/IGT
Plasma glucose concentrations (mmol/l)				
Fasting	4.8 ± 0.5*	6.3 ± 0.1†	5.2 ± 0.4‡	6.3 ± 0.2†
120-min	6.0 ± 1.1*	6.9 ± 1.1†	8.9 ± 0.9‡	9.4 ± 0.9‡
Plasma insulin concentrations (pmol/l)				
Fasting	210 ± 108*	366 ± 168†	294 ± 114‡	384 ± 114†
120-min	852 ± 642*	1,572 ± 600†	2,070 ± 1,176†	2,448 ± 1,440†

Data are means ± SD. Values not sharing a common symbol are significantly different ($P < 0.05$).

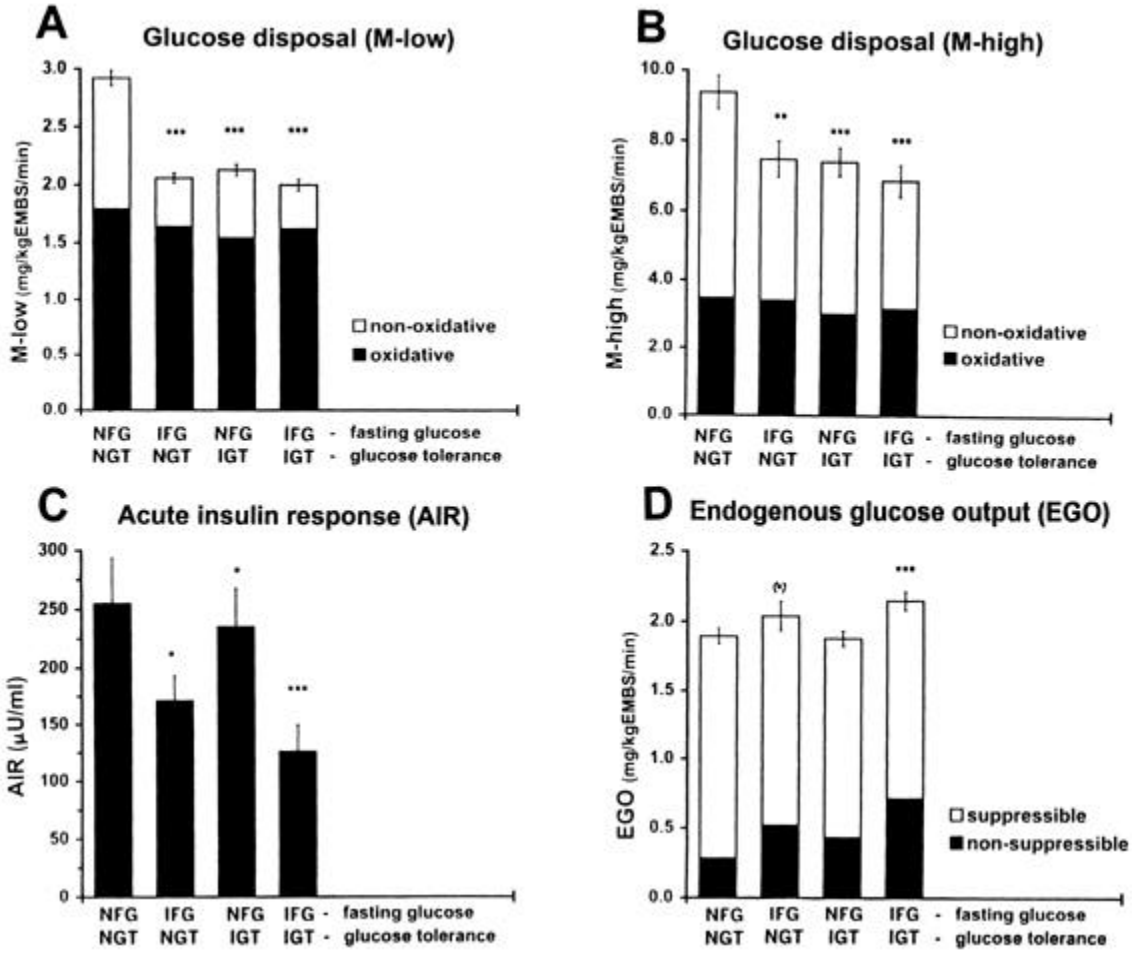

FIG. 1. Insulin-stimulated glucose disposal (*A* and *B*), AIR (*C*), and EGO (*D*) in 434 nondiabetic Pima Indians with either NFG or IFG (1997 ADA criteria [15]) and with either NGT or IGT (1985 WHO criteria [1]). Asterisks indicate significant differences compared with the control group with NFG/NGT (*left*): $^{(*)}P < 0.06$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. EMBS = fat-free mass + 17.7 kg.

cose homeostasis, EGO was higher in the IFG/NGT ($P = 0.05$) and IFG/IGT ($P < 0.0001$) groups than in the NFG/IGT group. After adjustment for age, sex, and percent body fat, EGO was only increased ($P < 0.001$) in the IFG/IGT group, and not in the IFG/NGT group, compared with the two groups with NFG. EGO was less suppressed at the end of the low-dose insulin infusion in the IFG/NGT (74%), NFG/IGT (77%), and IFG/IGT (67%) groups, compared with the NFG/NGT group (85%) (all $P < 0.05$) (Fig. 1*D*).

There was a positive curvilinear relationship between EGO and the fasting plasma glucose concentration ($r = 0.19$, $P < 0.01$), but no correlation between EGO and the 2-h plasma glucose concentration ($r = 0.03$, NS) (Fig. 2*D*).

DISCUSSION

Impaired insulin action, insulin secretory dysfunction, and increased EGO are the major metabolic abnormalities of type 2 diabetes (2,13,14). The first two of these abnormalities are often present in individuals with IGT. EGO, in contrast, is not increased in subjects with IGT, and is thus considered a later abnormality that occurs after the onset of diabetes (2,13,14). With the introduction of the new ADA diagnostic criteria in 1997 (15), impaired glucose homeostasis can now be defined not only by an impaired glucose response 2 h after an oral glucose load (7.8–11.1 mmol/l, IGT), but also by an impaired fasting plasma glucose concentration (6.1–7.0 mmol/l, IFG). Thus, if both WHO and ADA criteria are applied, impaired glucose homeostasis can be divided into three different subgroups.

The results of the present study in Pima Indians reveal both quantitative and qualitative differences in metabolic abnormalities among the three different subgroups of impaired glucose homeostasis. Pima Indians with isolated IFG and isolated IGT had a comparable impairment in insulin action, but those with isolated IFG had a greater impairment in early phase insulin secretion and, in addition, increased EGO compared with individuals with normal glucose homeostasis. In Pima Indians with combined IFG and IGT, even more profound abnormalities in insulin action, insulin secretion, and EGO were found. These differences between the different subgroups of impaired glucose homeostasis could be explained by the different relationships of early phase insulin secretion and EGO to the fasting versus the 2-h plasma glucose concentration.

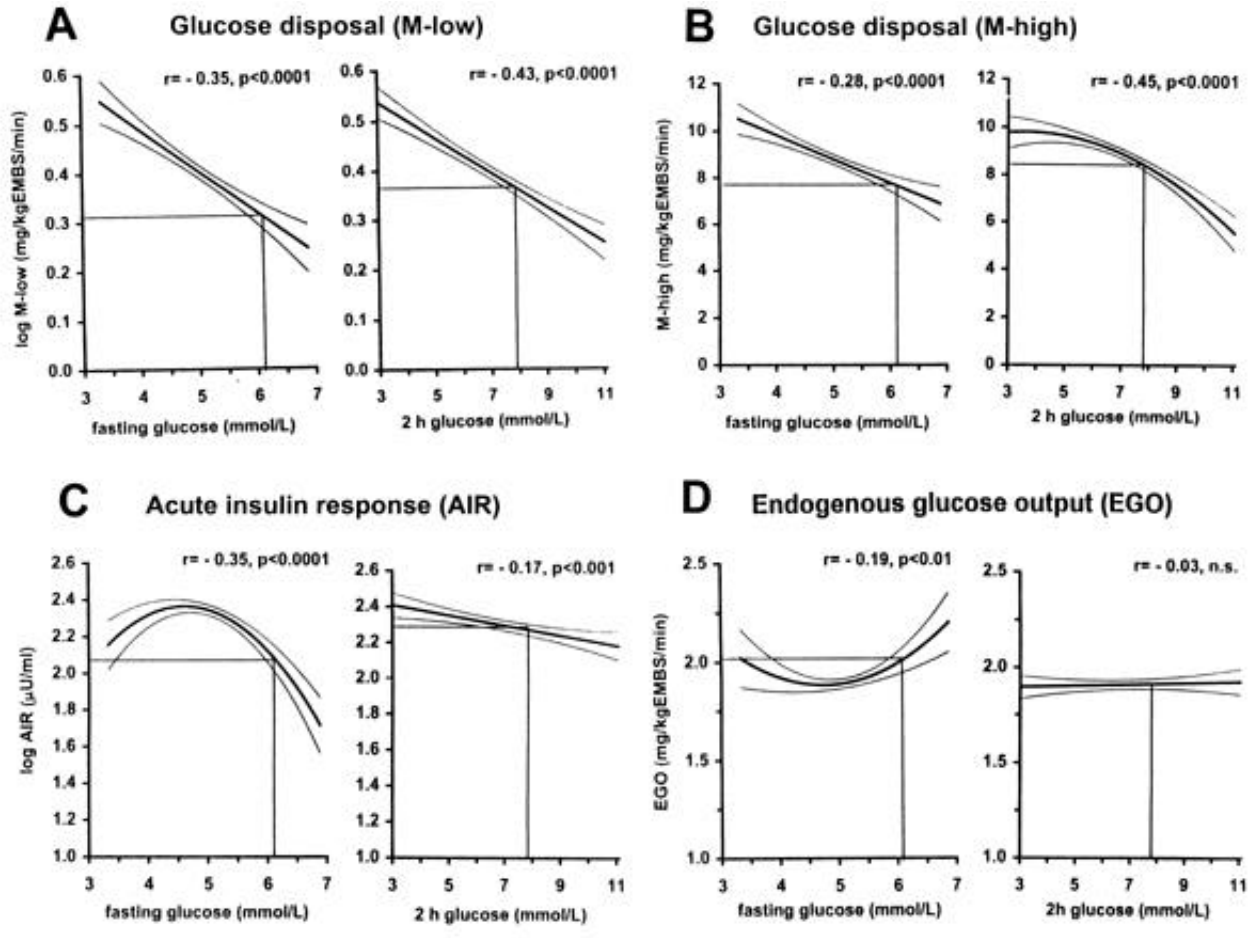

FIG. 2. Relationship of insulin-stimulated glucose disposal (*A* and *B*), AIR (*C*), and EGO (*D*) to the fasting and 2-h plasma glucose concentration in 434 nondiabetic Pima Indians. Results are given as the regression line and the upper and lower limits of the 95% CI of the regression line. EMBS = fat-free mass + 17.7 kg.

Obesity and older age are established risk factors for type 2 diabetes. It was, therefore, not unexpected that individuals from all three groups with impaired glucose homeostasis were older and more obese than individuals with NFG/NGT. The observation that Pima Indians with isolated IFG and combined IFG/IGT were heavier than those with isolated IGT differs from epidemiological findings in Caucasians, in which individuals with isolated IFG and isolated IGT showed similar anthropometric characteristics (36). To control for potential confounding effects, we performed all group comparisons with and without adjustment for age, sex, and percent body fat.

Insulin action. The present results confirm that individuals with IGT are more insulin resistant than individuals with NGT (2–7), as evidenced by a 27 and 21% lower insulin-stimulated glucose disposal at low- and high-dose insulin infusions, respectively. Individuals with isolated IFG showed a similar impairment in insulin action (–29% [*M*-low] and –20% [*M*-high]). The greatest decrease in glucose uptake was seen in individuals with combined IFG and IGT (–32% [*M*-low] and –27% [*M*-high]), although the magnitude of the defect was not significantly different from those in individuals with IFG or IGT alone. The finding that individuals with isolated IFG and isolated IGT showed a similar impairment in insulin action agrees with the results of our regression analyses, in which continua of fasting and 2-h glucose concentrations were used rather than arbitrary diagnostic categories. Both *M*-low and *M*-high were similarly negatively related to the fasting and the 2-h glucose concentrations. The decrease in insulin action in all three groups with impaired glucose homeostasis was almost exclusively accounted for by a lower rate of nonoxidative glucose disposal. This agrees with findings from previous studies (37,38) indicating that much of the insulin resistance in individuals with impaired glucose homeostasis and type 2 diabetes is due to an impaired stimulatory effect of insulin on skeletal muscle glycogenesis.

Insulin secretion. Whether insulin secretion is defective in individuals with impaired, but not diabetic, glucose homeostasis is controversial because results of studies of both early and late insulin responses are inconsistent (2,4,6–11). This may be attributable to ethnic and methodological differences (8–10) and the uncertainty, inherent in cross-sectional studies, concerning how many individuals with IGT will ultimately progress to diabetes. In the present study, Pima Indians with isolated IGT had a relatively mild defect in AIR (–8%) that was significant, however, when adjusted for insulin

action. The importance of interpreting insulin secretion relative to the degree of insulin resistance has been previously pointed out (39,40). A greater defect in AIR is found in Pima Indians with IGT who later progress to diabetes, as we recently demonstrated in a longitudinal study in this population (41). Interestingly, Pima Indians with isolated IFG showed a more pronounced defect in AIR (–33%) than did individuals with isolated IGT. This was explained by the finding that AIR was more closely related to the fasting than to the 2-h glucose concentration and that the relationship to fasting glucose was curvilinear rather than linear. Our results, therefore, confirm the notion of O'Rahilly et al. (22), who suggested that AIR is more closely related to the fasting than to the 2-h glucose concentration. An even more severe impairment in early insulin secretion was present in Pima Indians with combined IFG and IGT. In these individuals, AIR was reduced to as much as half of the average AIR in individuals with normal glucose homeostasis. Fasting and 2-h insulin concentrations were increased in all three groups with impaired glucose homeostasis, compared with the control group. Hyperinsulinemia is a common metabolic characteristic of individuals with IGT (2,3,13,14), and our results indicate that this is also true in individuals with IFG. Upon closer scrutiny, the highest fasting insulin concentrations were found in individuals with IFG, irrespective of whether glucose tolerance was normal or impaired, whereas the highest 2-h insulin concentrations were found in individuals with IGT. This observation is likely due to the higher prevailing fasting and 2-h glucose concentrations in these groups because glucose is the major physiological stimulus of insulin secretion (40).

Endogenous glucose output. Our finding of normal basal EGO in Pima Indians with isolated IGT agrees with previous studies, demonstrating increased basal EGO only in individuals with diabetes (2,12–14). However, and probably the most significant finding, our analysis revealed that EGO is increased in nondiabetic Pima Indians with IFG. This increase was evident in individuals with isolated IFG (8%), and was even more pronounced in those with additional IGT (13%). Moreover, individuals from all three groups with impaired glucose homeostasis showed reduced suppression of EGO under physiological levels of hyperinsulinemia. Thus, in Pima Indians, hepatic insulin resistance appears to be a common characteristic of impaired glucose homeostasis, present in individuals with IFG and/or IGT, whereas basal EGO is increased only in individuals with IFG. Presumably, the high fasting insulin concentration prevents an increase in basal EGO in Pima Indians with IGT, but not in those with IFG. In individuals with type 2 diabetes, increased EGO is considered to be a major mechanism underlying the development of fasting hyperglycemia (2,14,42). It is thus likely that the increased EGO also contributes to the mildly elevated fasting glucose concentration in individuals with IFG. In accordance with the differences in basal EGO between individuals with IGT and IFG, there was no relationship between EGO and the 2-h glucose concentration, but there was a positive curvilinear relationship between EGO and the fasting glucose concentration, even within the nondiabetic range.

Together, the above findings demonstrate that significant derangements in the regulation of EGO can occur in people without diabetes. This is supported by reports of increased EGO in nondiabetic first-degree relatives of individuals with type 2 diabetes (43) and in nondiabetic Australian Aborigines (44), another ethnic group with a high incidence of diabetes. Abnormalities in hepatic glucose regulation have also been demonstrated in nondiabetic African-Americans, who are also at a high risk for diabetes (45), but not in most studies in Caucasians (7,46). One might speculate, based on these findings, that abnormalities in hepatic glucose regulation may play a causal role in the pathogenesis of type 2 diabetes, particularly in ethnic minorities with a propensity for diabetes. However, in the only prospective study in which this question was examined, basal EGO was not predictive of diabetes in Pima Indians (23). In this study, decreased suppression of EGO by insulin was a weak predictor of diabetes, but not after adjusting for obesity (23). Further studies are warranted to compare insulin action, insulin secretion, and EGO in individuals with IFG and/or IGT in other populations. Such studies may help to identify the most effective strategies to prevent diabetes in individuals with different phenotypes of impaired glucose homeostasis and in different ethnic groups.

Our findings suggest that the fasting glucose concentration and the oral glucose tolerance test are both useful diagnostic tools, since the two tests in combination allow stratification of individuals with impaired glucose homeostasis into subgroups with different metabolic abnormalities. This distinction may have important clinical implications, such as in the choice of strategies to prevent diabetes. Several studies are currently underway of the prevention of type 2 diabetes in individuals with impaired glucose homeostasis using different pharmacological and nonpharmacological interventions (47–49). Our results suggest that the efficacy of different strategies to prevent diabetes may differ between different subgroups of impaired glucose homeostasis. For instance, drugs that may, in part, restore a normal insulin secretion pattern, such as fast-acting insulin secretagogues, may be more effective in individuals with IFG than in those with IGT. Whether drugs that act via suppression of EGO, such as the biguanides, will prevent diabetes in individuals with impaired glucose homeostasis remains to be seen (47). While especially individuals with IFG have clear abnormalities in hepatic glucose regulation, increased basal EGO does not seem to be a predictor of diabetes (23). Importantly, sustained weight reduction is associated with improvements in both insulin action and early-phase insulin secretion in Pima Indians with impaired glucose homeostasis (50), emphasizing the potential of nonpharmacological prevention strategies. In the end, the utility of different approaches to prevent diabetes can only be established in intervention studies.

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