

# Insulin Resistance and Insulin Secretory Dysfunction Are Independent Predictors of Worsening of Glucose Tolerance During Each Stage of Type 2 Diabetes Development

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**OBJECTIVE** — Although prospective studies indicate that insulin resistance and insulin secretory dysfunction predict type 2 diabetes, they provide limited information on the relative contributions of both abnormalities to worsening glucose tolerance at different developmental stages of the disease. We therefore assessed the predictive effect of insulin resistance and insulin secretory dysfunction separately for the progression from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) and from IGT to diabetes.

**RESEARCH DESIGN AND METHODS** — Insulin-stimulated glucose disposal ( $M$ ) (hyperinsulinemic clamp), acute insulin secretory response (AIR) (25-g intravenous glucose tolerance test), and body composition (hydrodensitometry or dual-energy X-ray absorptiometry) were measured in 254 Pima Indians with NGT and in 145 Pima Indians with IGT, who were then followed for 0.5–13 years.

**RESULTS** — After follow-ups of  $4.4 \pm 3.1$  and  $5.5 \pm 3.4$  years, 79 (31%) of the subjects with initial NGT had developed IGT, and 64 (44%) of the subjects with initial IGT had developed diabetes. In proportional-hazards analyses with adjustment for age, sex, and percent body fat, low  $M$  and low AIR were independent predictors of both the progression from NGT to IGT (relative hazards [95% CI] for 10th vs. 90th percentile:  $M$  2.4 [1.2–4.7],  $P < 0.02$ ; AIR 2.1 [1.1–4.1],  $P < 0.04$ ) and from IGT to diabetes ( $M$  2.5 [1.3–5.0],  $P < 0.01$ ; AIR 1.8 [0.99–3.3],  $P = 0.055$ ).

**CONCLUSIONS** — During each stage of the development of type 2 diabetes, insulin resistance and insulin secretory dysfunction are independent predictors of worsening glucose tolerance and are, therefore, both targets for the primary prevention of the disease.

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The development of type 2 diabetes is characterized by a progressive deterioration of glucose tolerance from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) to diabetes. Typically, this deterioration will last several years (1).

Defects in insulin action and insulin secretion are the major metabolic abnormalities underlying this progression (1–5). To develop effective strategies for the primary prevention of type 2 diabetes, it is important to understand the relative importance of

insulin resistance and insulin secretory dysfunction during the different stages of disease development.

Although it has long been recognized in cross-sectional studies that both abnormalities can be present in individuals with impaired but not yet diabetic glucose homeostasis, it was not until prospective (1–6) and longitudinal (6,7) data became available that the pathogenetic importance of insulin resistance and insulin secretory dysfunction was further established. The prospective studies provided evidence that insulin resistance and insulin secretory dysfunction predict the development of type 2 diabetes in various populations (1–6). However, because most studies included individuals with NGT and IGT at baseline and used indirect measures of insulin action and insulin secretion, mostly derived from oral glucose tolerance tests (OGTTs), their results give only very limited information about the relative contributions of both abnormalities to the worsening of glucose tolerance at different stages of the disease.

The high incidence of type 2 diabetes in the Pima Indians of Arizona has made feasible prospective and longitudinal studies with a more detailed metabolic characterization that includes the assessment of insulin action and early-phase insulin secretion by hyperinsulinemic-euglycemic clamps and intravenous glucose tolerance tests, respectively (1,5,7). Earlier prospective results of this study revealed that in individuals with NGT, a low rate of insulin-stimulated glucose disposal ( $M$ ) and a lower acute insulin secretory response (AIR) to an intravenous glucose challenge are independent and additive predictors of the development of diabetes (1,5). More recent longitudinal analyses have revealed that both abnormalities deteriorate progressively as individuals make the transition from NGT to IGT to diabetes (7). The latter finding raises the important question of whether insulin resistance and insulin secretory dys-

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**Abbreviations:** AIR, acute insulin secretory response; EGO, endogenous glucose output; EMBS, estimated metabolic body size; IGT, impaired glucose tolerance;  $M$ , insulin-stimulated glucose disposal; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Baseline characteristics and follow-up data of the study populations

	Progression from NGT to IGT				Progression from IGT to diabetes			
	Entire population	Progressors (IGT at follow-up)	Nonprogressors (NGT at follow-up)	P*	Entire population	Progressors (diabetes at follow-up)	Nonprogressors (NGT/IGT at follow-up) (49/32 NGT/IGT)	P*
n	254	79	175	—	145	64	81	—
F/M	81/173	23/56	58/117	—	83/62	39/25	43/38	—
Age (years)	26.4 ± 6.1	26.1 ± 5.5	26.5 ± 6.3	0.61	29.5 ± 5.8	29.4 ± 5.9	29.6 ± 5.8	0.81
Height (cm)	168 ± 8	167 ± 7	168 ± 8	0.29	164 ± 8	164 ± 8	164 ± 9	0.60
Body weight (kg)	92.6 ± 22.7	93.9 ± 22.4	92.0 ± 22.8	0.61	99.0 ± 21.2	103.7 ± 21.3	95.4 ± 20.2	<0.01
Body fat (%)	31 ± 8	31 ± 9	32 ± 7	0.26	36 ± 7	37 ± 7	35 ± 7	0.09
Fat mass (kg)	29.6 ± 12.7	30.4 ± 13.3	29.2 ± 12.8	0.40	36.3 ± 12.1	39.2 ± 12.6	34.2 ± 11.2	<0.02
Fat-free mass (kg)	63.0 ± 12.7	63.5 ± 12.5	62.8 ± 12.8	0.96	62.7 ± 12.5	64.5 ± 12.6	61.2 ± 12.3	<0.01
Waist-to-thigh ratio	1.63 ± 0.15	1.63 ± 0.14	1.63 ± 0.15	0.99	1.69 ± 0.15	1.70 ± 0.15	1.67 ± 0.15	0.14
Fasting glucose (mmol/l)	4.9 ± 0.4	5.0 ± 0.5	4.8 ± 0.4	<0.001	5.3 ± 0.5	5.5 ± 0.4	5.1 ± 0.5	<0.001
2-h glucose (mmol/l)	6.1 ± 1.1	6.3 ± 0.8	5.9 ± 1.1	<0.001	8.9 ± 0.9	9.1 ± 0.8	8.7 ± 0.7	<0.02
Fasting insulin (pmol/l)	216 ± 102	216 ± 90	216 ± 102	0.07†	288 ± 114	294 ± 108	276 ± 114	0.26†
2-h insulin (pmol/l)	894 ± 648	948 ± 582	870 ± 672	0.27†	1,974 ± 1,158	1,944 ± 1,104	1,998 ± 1,194	0.10†
M (mg/kg EMBS per min)	2.8 ± 1.1	2.5 ± 0.8	2.9 ± 1.3	<0.05‡	2.2 ± 0.5	2.1 ± 0.5	2.3 ± 0.5	<0.03‡
AIR (pmol/l)	1,518 ± 936	1,446 ± 822	1,548 ± 984	0.10†	1,302 ± 744	1,128 ± 642	1,434 ± 792	<0.05†
Basal EGO (mg/kg EMBS per min)	1.91 ± 0.24	1.87 ± 0.23	1.92 ± 0.24	0.08	1.94 ± 0.24	1.86 ± 0.24	1.98 ± 0.22	<0.01
EGO suppression (%)	82 ± 18	82 ± 21	82 ± 19	0.92	74 ± 19	73 ± 21	75 ± 19	0.50
Follow-up duration (years)	4.4 ± 3.1	3.9 ± 2.7	4.7 ± 3.2	0.08	5.5 ± 3.4	5.1 ± 3.3	5.8 ± 3.5	0.24
Follow-up 2-h glucose (mmol/l)	6.7 ± 1.8	8.8 ± 0.8	5.8 ± 1.1	<0.0001	10.4 ± 4.3	14.0 ± 3.8	7.4 ± 1.7	<0.0001

Data are means ± SD (unadjusted values). P values indicate significant differences between progressors and nonprogressors. \*All comparisons adjusted for age and sex; †additionally adjusted for percent body fat and M; ‡additionally adjusted for percent body fat.

function remain independent predictors of diabetes once individuals have developed IGT or whether one abnormality becomes relatively more important than the other. An earlier prospective study in Pima Indians, in which insulin action and insulin secretion were estimated from fasting and postchallenge plasma insulin concentrations during an OGTT, suggested that insulin resistance might play a predominant role in the development of IGT, whereas insulin secretory dysfunction might be the major factor determining whether individuals with IGT progress to diabetes (6). Studies in other populations, however, found that a low early-phase insulin secretion predicted the transition from NGT to IGT (8) and that insulin resistance predicted the progression from IGT to diabetes (1,2). One explanation for these discrepancies could be that the correlations of OGTT-derived measures of insulin action and insulin secretion with M and AIR are generally not very strong (correlation coefficients 0.2–0.6) (9). This makes it difficult to estimate the relative contributions of insulin resistance and insulin secretory dysfunction in the development of diabetes from OGTT-derived indexes alone.

To determine whether low M and low AIR predict worsening glucose tolerance differently during the progression from NGT to IGT and from IGT to diabetes, we analyzed prospective data from a large number of Pima Indians in whom body composition, insulin action, and insulin secretion had been measured on a baseline occasion and who were then followed for up to 13 years.

**RESEARCH DESIGN AND METHODS**

Subjects in this study were Pima (or closely related Tohono O’odham) Indians from the Gila River Indian Community near Phoenix, Arizona, who participated in an ongoing longitudinal study of the pathogenesis of type 2 diabetes, as described in detail elsewhere (5,7). In brief, subjects with either NGT or IGT were admitted for 8–15 days to the Clinical Research Unit of the National Institutes of Health in Phoenix. After at least 3 days on a weight-maintaining diet, a series of tests was conducted to assess body composition, glucose tolerance, insulin action, insulin secretion, and endogenous glucose output (EGO) (5,7). Body composition was estimated by underwater weighing with simultaneous

determination of residual lung volume by helium dilution (10) or by total-body dual-energy X-ray absorptiometry (DPX-L; Lunar Radiation, Madison, WI) (11). A previously published conversion equation derived in our unit was used to make measurements of body composition comparable between the two methods (11). Waist and thigh circumferences were measured and used to calculate the waist-to-thigh ratio as an index of body fat distribution. Glucose tolerance was determined by a 75-g OGTT with measurement of fasting and 2-h glucose and insulin concentrations (5,7) and classified according to the 1985 World Health Organization diagnostic criteria (12). On a separate day, in the morning after a 12-h fast, the rate of basal EGO was determined using a primed (30 µCi) continuous (0.3 µCi per min) [3-H<sup>3</sup>]glucose infusion as described (5,7). After a 100-min baseline period, a hyperinsulinemic-euglycemic clamp was initiated (100-min insulin infusion at a rate of 40 mU · m<sup>-2</sup> · min<sup>-1</sup>, achieving a steady-state plasma insulin concentration of 840 ± 252 pmol/l) (5,7). The [3-H<sup>3</sup>]glucose infusion was continued during the clamp. From the rate of exogenous glucose

infused and the measured rate of endogenous glucose produced during the last 40 min of the clamp, the rate of total insulin-stimulated glucose disposal ( $M$ ) was calculated and adjusted for the steady-state glucose and insulin concentrations (5,7). Suppression of EGO at the end of the clamp was expressed as the percent change from baseline.  $M$  and EGO were normalized to estimated metabolic body size (EMBS), which is directly derived from fat-free mass but takes into account the intercept of the relation between metabolic rate and fat-free mass ( $-17.7$  kg in our laboratory [i.e.,  $EMBS = \text{fat-free mass} + 17.7$  kg]) (13). Insulin secretion was measured in response to a 25-g intravenous glucose tolerance test with calculation of the AIR as the average incremental plasma insulin concentration from the third to the fifth minute after the glucose bolus (5,7). Subjects were then invited back at approximately annual intervals for repeat OGTTs to assess how many individuals with NGT and IGT at baseline had developed IGT and diabetes, respectively (progressors). In subjects with repeated worsening and improvement of glucose tolerance status, only the first occurrence of IGT and/or diabetes was considered. Subjects with NGT at baseline and diabetes at follow-up were not included in the present analyses, whereas subjects who had been studied at each stage of the progression from NGT to IGT to diabetes were included in both analyses. Except for obesity and diabetes, all subjects were healthy according to a comprehensive medical history, physical examination, and routine blood and laboratory tests, and none smoked or took medications at the time of their studies. The study protocol was approved by the Institutional Review Board of the National Institutes of Diabetes and Digestive and Kidney Diseases and by the Tribal Council of the Gila River Indian Community. All subjects gave written informed consent before participation.

Statistical analyses were performed using the procedures of the SAS Institute (Cary, NC). Results are given as means  $\pm$  SD. For all statistical analyses,  $M$  and AIR were log-transformed to achieve a normal distribution and to account for the hyperbolic relationship between both measures. General linear regression models were used to compare baseline characteristics between progressors and nonprogressors with adjustment for age and sex. Because measurements of insulin secretion need to be interpreted on the basis of underlying

**Table 2—Multivariate proportional-hazards analyses of predictors of the progression from NGT to IGT and from IGT to diabetes in Pima Indians**

Predictor variable	Value at 10th percentile	Value at 90th percentile	Relative hazard†	95% CI	P
Progression from NGT to IGT					
Sex (M/F)			0.6	0.3–1.2	NS
Age (years)	19	36	1.0	0.6–1.9	NS
Body fat (%)	21	41	1.7	0.8–3.0	NS
$M$ (mg/kg EMBS per min)*	1.9	4.1	2.4	1.2–4.7	<0.02
AIR (pmol/l)*	618	2,856	2.1	1.1–4.1	<0.04
Progression from IGT to diabetes					
Sex (M/F)			0.6	0.4–1.2	NS
Age (years)	22	38	0.9	0.5–2.0	NS
Body fat (%)	26	45	1.5	0.6–3.6	NS
$M$ (mg/kg EMBS per min)*	1.8	4.3	2.5	1.3–5.0	<0.01
AIR (pmol/l)*	570	2,820	1.8	0.99–3.3	0.055

Relative hazards were calculated with all five variables in the same model (i.e., the predictive effects of  $M$  and AIR are adjusted for age, sex, and percent body fat). \*The value at the 10th percentile is the value associated with the higher risk of developing IGT and diabetes, respectively; †hazard rate for a subject at the percentile associated with the higher risk divided by the hazard rate for a subject at the percentile associated with the lower risk.

insulin sensitivity (7,14,15), all insulin concentrations (fasting, 2-h, and AIR) were also adjusted for  $M$  and percent body fat, in addition to age and sex (Table 1). Risk factors for progression from NGT to IGT and from IGT to diabetes were estimated by multivariate proportional-hazards analysis (5). First, the relative hazards of  $M$  and AIR were evaluated at the 10th and 90th percentiles of the predictor variables with additional adjustment for age, sex, and percent body fat (Table 2). In addition, risk factors were assessed by stratification. With the study populations subdivided into subjects with  $M$  and AIR above and below the median, respectively, the 4-year cumulative incidence rates of progression from NGT to IGT and from IGT to diabetes were estimated by the Kaplan-Meier method (5) with simultaneous adjustment for age, sex, and percent body fat (Fig. 1).

**RESULTS** — The baseline characteristics of the two study populations, the mean follow-up duration, and the mean 2-h glucose concentration at follow-up are shown in Table 1.

#### Progression from NGT to IGT

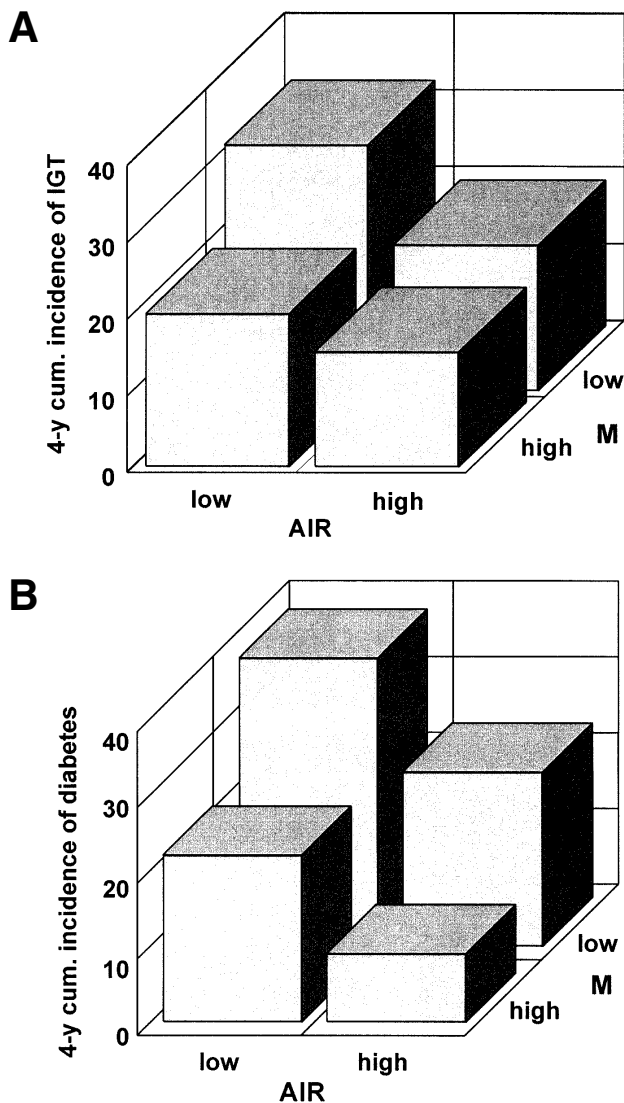
Among the 254 subjects with initial NGT, 79 (31%) had developed IGT at follow-up, whereas 175 subjects (69%) were still with NGT. Age, height, weight, adiposity, waist-to-thigh ratio, and fasting and 2-h plasma insulin concentrations at baseline were not different between the two groups, nor was

the average follow-up duration (Table 1). However, subjects who developed IGT had higher fasting and 2-h plasma glucose concentrations and a lower  $M$  at baseline than those who maintained NGT, whereas AIR and basal EGO only tended to be lower (Table 1).

In a proportional-hazards analysis with adjustment for age, sex, and percent body fat, low  $M$  and low AIR were independent predictors of the progression from NGT to IGT (Table 2 and Fig. 1A). Accordingly, after adjustment for age, sex, and percent body fat, individuals with both  $M$  and AIR below the median had the highest 4-year cumulative incidence of IGT, whereas those with  $M$  and AIR above the median had the lowest incidence (Fig. 1A). Subjects with  $M$  below but AIR above the median and with  $M$  above but AIR below the median had a comparable intermediate risk of developing IGT (Fig. 1A).

#### Progression from IGT to diabetes

Among the 145 subjects with initial IGT, 64 (44%) had developed diabetes at follow-up. Of the remaining 81 subjects, 32 (22%) remained as having IGT, and 49 (34%) had reverted to NGT. Age, height, weight, adiposity, waist-to-thigh ratio, and fasting and 2-h plasma insulin concentrations at baseline and the follow-up duration were not different between subjects who developed diabetes and those who did not develop diabetes (Table 1). Subjects who maintained IGT and those who reverted to NGT did not



**Figure 1**—A: Progression from NGT to IGT. Four-year cumulative incidence of IGT in 254 Pima Indians with initial NGT as a function of insulin action (M) and early-phase insulin secretion (AIR) at baseline. B: Progression from IGT to type 2 diabetes. Four-year cumulative incidence of type 2 diabetes in 145 Pima Indians with initial IGT as a function of insulin action (M) and early-phase insulin secretion (AIR) at baseline. In both graphs, subjects are divided into those with M and AIR above and below the median.

differ in any baseline characteristics and were thus pooled in a group of nonprogressors. Subjects who developed diabetes at follow-up had higher fasting and 2-h plasma glucose concentrations, lower M, lower AIR, and lower basal EGO at baseline compared with those who did not (Table 1).

In a proportional-hazards analysis with adjustment for age, sex, and percent body fat, low M and low AIR were independent predictors of the progression from IGT to diabetes (Table 2, Fig. 1B). Accordingly, after adjustment for age, sex, and percent body fat, individuals with both M and AIR below

the median had the highest 4-year cumulative incidence of diabetes, whereas subjects with both M and AIR above the median had the lowest incidence (Fig. 1B). As with the progression from NGT to IGT, subjects with M below but AIR above the median and with M above but AIR below the median had a comparable intermediate risk of progressing from IGT to diabetes (Fig. 1B).

**Other factors**

Although fasting plasma glucose concentration and basal EGO were different between the progressors and nonprogressors at base-

line, neither of these variables was a significant independent predictor of worsening glucose tolerance when added to age, sex, percent body fat, M, and AIR in the proportional-hazard models. Conversely, AIR and M remained significant predictors after inclusion of these variables.

**CONCLUSIONS**

Numerous prospective studies in various populations indicate that insulin resistance and insulin secretory dysfunction predict the development of type 2 diabetes (1–6). However, the majority of these studies included both individuals with NGT and IGT at baseline and used indirect measures of insulin action and insulin secretion derived from an OGTT. Moreover, to date, only two groups of investigators have examined the metabolic predictors of progression from NGT to IGT (6,8). Thus, although these studies provide evidence for a pathogenic role of insulin resistance and insulin secretory dysfunction in the development of type 2 diabetes, they give only limited information as to the relative importance of these abnormalities during the different stages of the development of the disease.

In the present study, we addressed this question by assessing the predictive effects of insulin resistance and low early-phase insulin secretion separately for the progression from NGT to IGT and also from IGT to diabetes, using direct measures of insulin action and insulin secretion derived from hyperinsulinemic clamps and intravenous glucose tolerance tests, respectively. We found that a low rate of M and a lower AIR were independent predictors of both the transition from NGT to IGT and the progression from IGT to diabetes. These results indicate that insulin resistance and insulin secretory dysfunction have independent and additive pathogenic roles during each stage of the development of type 2 diabetes.

We have previously reported that low M and low AIR predict the development of type 2 diabetes in Pima Indians with NGT at baseline (5). It was therefore not unexpected that both abnormalities also predict the progression from NGT to IGT. This could not have been concluded from the former finding, however, because it was possible that either abnormality would not be predictive until individuals developed IGT. In fact, the latter was suggested by findings from a previous prospective study in a large number of Pima Indians, in which estimates of insulin action and insulin secretion were derived from an OGTT (6). In

that study, insulin resistance, as inferred from a high fasting insulin concentration, was predictive of the progression from NGT to IGT, whereas insulin secretory dysfunction, as inferred from a low 2-h plasma insulin concentration, was not predictive (6). Because AIR represents a measure of early-phase insulin secretion, whereas the 2-h plasma insulin concentration represents a measure of late-phase insulin secretion, both variables being rather weakly related with one another ( $r = \sim 0.2$ ) (9), these previous observations do not contradict the present findings. In fact, it has been shown experimentally that inhibition of early-phase insulin secretion is associated with increased 2-h insulin concentrations (16), whereas augmentation of early-phase insulin secretion leads to a reduction in 2-h postprandial insulin concentrations (17). On the other hand, our findings appear to agree with those of the San Antonio Heart Study (8), in which a high fasting insulin concentration (a surrogate marker of insulin resistance) and a low incremental 30-min insulin concentration (an indicator of early-phase insulin secretory dysfunction) were independent predictors of the progression from NGT to IGT in a Mexican-American population. The 30-min insulin concentration during an OGTT is more closely related to the AIR ( $r = \sim 0.4$ ) than the 2-h insulin concentration (9). However, when we used the incremental 30-min insulin concentration from the OGTT (adjusted for the 30-min glucose concentration), instead of the AIR in our proportional-hazards analyses, a low incremental 30-min insulin concentration was predictive of progression from IGT to diabetes only, but not of progression from NGT to IGT (data not shown).

Although the above results further support our previous findings (5) that primary defects in insulin action and insulin secretion predispose individuals with NGT to worsening glucose tolerance, we have recently shown that transition from NGT to IGT is accompanied by further secondary deteriorations of both insulin resistance and insulin secretory dysfunction (7). This raises the important question as to whether both abnormalities would maintain the pathogenic roles or whether one abnormality would become the predominant pathogenic factor while the other one loses its predictive effect. Previous prospective studies using indirect measures of insulin action and insulin secretion have been inconclusive in this respect (1,2,6). With our second prospective analysis of the predictors of pro-

gression from IGT to diabetes, we have now established that low *M* and low AIR remain independent and additive predictors of worsening of glucose tolerance in Pima Indians once individuals have developed IGT. This indicates that both insulin resistance and insulin secretory dysfunction maintain independent pathogenic roles as glucose tolerance worsens. This finding may have important implications for the development of effective strategies for the primary prevention of type 2 diabetes.

Increased basal EGO and impaired suppression of EGO by insulin infusion or glucose ingestion are also common abnormalities of type 2 diabetes (1,2,18–20). Although most studies have found increased basal EGO only in individuals with diabetes (1,2), recent studies in Pima Indians (18) and other populations (20) indicated that basal EGO can be increased in certain subgroups of nondiabetic individuals with high diabetes risk, such as those with impaired fasting glucose (18) or first-degree relatives of people with type 2 diabetes (20). In the present prospective analysis, however, individuals who progressed from NGT to IGT and from IGT to diabetes had lower, not higher, basal EGO at baseline compared with those who did not progress. After accounting for *M* and AIR in a proportional-hazard model, however, the lower rates of basal EGO in the progressors were not predictive of worsening of glucose tolerance. Impaired suppression of EGO by insulin infusion or glucose ingestion is a more common abnormality in individuals with impaired glucose homeostasis than elevated basal EGO (1,2,19). Some authors have provided evidence that this impairment might be the major cause of postprandial hyperglycemia in individuals with IGT (19). As with basal EGO, however, in the present prospective study, the suppression of EGO by insulin was not predictive of worsening of glucose tolerance. However, it is possible that the marked (>80%) average suppression of EGO at the end of the clamp had precluded the detection of more subtle differences in hepatic insulin sensitivity between progressors and nonprogressors. Combined, the above findings are consistent with our previous conclusion (5,7) that abnormal regulation of EGO plays no major role in the development of diabetes in Pima Indians.

In summary, the present study of a large number of Pima Indians followed prospectively over several years showed that a low rate of *M* and a low AIR to glu-

cose are independent and additive predictors of both the transition from NGT to IGT and the progression from IGT to diabetes. These findings indicate that insulin resistance and insulin secretory dysfunction play pathogenic roles during each stage of the development of type 2 diabetes and are therefore both targets for the primary prevention of the disease.

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