Development of Impaired Glucose Tolerance With or Without Weight Gain

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OBJECTIVE — To evaluate whether risk factors and changes in insulin concentrations differ in subjects who develop impaired glucose tolerance with or without weight gain. Hyperinsulinemia is a risk factor for impaired glucose tolerance, and insulin concentrations increase further with the development of impaired glucose tolerance. Its development, however, often is accompanied by weight gain, which, by itself, is associated with high insulin concentrations.

RESEARCH DESIGN AND METHODS — Participants for this study were adult Pima Indians involved in an ongoing epidemiological study. Initially, all had normal glucose tolerance. During follow-up, 80 of 387 who did not gain weight developed impaired glucose tolerance, as did 295 of 1026 who gained weight. Risk factors for impaired glucose tolerance and the relationships between changes in weight and glucose and changes in insulin were evaluated by multivariate analyses.

RESULTS — High baseline fasting insulin predicted impaired glucose tolerance regardless of weight after adjustment for age, sex, body mass index, and glucose. The development of impaired glucose tolerance was accompanied by a further increase in fasting and 2-h insulin, whether or not subjects gained weight. In both weight-change groups, impaired glucose tolerance was associated with more centralized fat distribution.

CONCLUSIONS — Fasting hyperinsulinemia, a reflection of insulin resistance, is associated with the risk of developing impaired glucose tolerance whether or not weight is gained. Impaired glucose tolerance occurs when insulin resistance increases further. Weight gain is the most common precipitating factor. Aging and physical inactivity are other possible precipitating factors.

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IGT, IMPAIRED GLUCOSE TOLERANCE; NGT, NORMAL GLUCOSE TOLERANCE; BMI, BODY MASS INDEX; OGTT, ORAL GLUCOSE TOLERANCE TEST; FPG, FASTING PLASMA GLUCOSE; RIA, RADIOIMMUNOASSAY; CV, COEFFICIENT OF VARIATION; CI, CONFIDENCE INTERVAL.

Most subjects with IGT are more obese and insulin resistant than those with NGT (1). Longitudinal studies show that obesity and a high insulin concentration are risk factors for transition from NGT to IGT (2). This association, however, may be an effect of the weight gain that often accompanies the development of IGT in aggravating insulin resistance. Thus, insulin may play a different role in subjects who develop IGT without gaining weight.

RESEARCH DESIGN AND METHODS

— Study participants were Pima Indians involved in an ongoing epidemiological study in the Gila River Indian Community of Arizona. Every other year, they are invited for examinations that include a medical history and measurements of height and weight. Recently, waist and thigh girths also have been measured. During a 75-g OGTT, venous blood was drawn for determination of FPG and 2-h plasma glucose and fasting and 2-h serum insulin concentrations. Plasma glucose concentrations were measured with an autoanalyzer. Serum insulin concentrations were measured in order of sampling by RIA (3) with an interassay CV of 6–8%.

All subjects in this study had at least two examinations after they reached 18 yr of age. At the first examination (baseline examination), they had normal OGTTs (FPG and 2-h plasma glucose <7.8 mM). They were classified at follow-up examination(s) according to glucose tolerance and changes in weight from the baseline examination.

The weight-change categories were defined as weight gain if the subjects gained weight between the baseline and follow-up examination(s) (n = 1026) and no weight gain if they maintained or lost weight (n = 387). Glucose tolerance was categorized as normal or impaired (2-h plasma glucose ≥ 7.8 and < 11.1 mM [4]). Subjects who developed diabetes (2-h glucose ≥11.1 mM [4]) were included in

Table 1—*Baseline characteristics and end points of subjects who did or did not gain weight during the follow-up*

	Subject groups	
	No weight gain	Weight gain
N	387	1026
Age (yr), mean (range)	32.8 (18–81)	27.0 (18–86)
F/M (% F)	246;141 (64)	667;359 (65)
BMI (kg/m^2)*	31.1 ± 7.0	30.3 ± 6.8
FPG (mM)*	5.20 ± 0.51	5.12 ± 0.50
2-h glucose (mM)*	5.91 ± 1.06	5.74 ± 1.10
Fasting insulin (pM)†	140 (41–480)	134 (41–444)
2-h insulin (pM)†	584 (142–2395)	523 (123–2231)
Follow-up (yr), mean (range)	4.9 (1.4–15.4)	7.1 (1.5–17.9)
End-point status (NGT/IGT)	307;80	731;295

*Data are means ± SD.
†Mean and 95% CI for individuals computed after logarithmic transformation, but shown on the original scale.

the analysis only if they had at least one nondiabetic follow-up examination. Of the potentially eligible subjects, 78 (5.8%) had diabetes at the first follow-up examination and were excluded.

Statistical analysis

Risk factors for IGT were assessed with the proportional hazards model. The statistical significance of changes in insulin concentrations during follow-up was tested with a paired Student's *t* test. Multiple linear regression was used to predict changes in insulin concentration as a function of glucose and weight changes. Logarithmic transformation was used to normalize insulin distributions.

RESULTS — Subject characteristics are shown in Table 1. The average weight change was −4.3 kg in subjects without weight gain and 11.6 kg in those who gained weight.

Risk factors for IGT

A high baseline fasting insulin concentration, adjusted for age and sex, predicted IGT in patients who did or did not gain weight (Table 2) and remained significant when adjusted for 2-h glucose and BMI. A high baseline 2-h insulin concentration significantly predicted IGT only in subjects who gained weight.

Changes in insulin concentration with the development of IGT

The changes in insulin concentrations during the development of IGT are shown in Fig. 1 in both weight-change groups, according to age at baseline (<40 yr of age or ≥40 yr of age). Baseline fasting and 2-h insulin concentrations were not significantly different among the four groups. Each group experienced a significant increase in mean 2-h insulin concentration. Fasting insulin significantly increased in subjects who developed IGT and gained weight but not in those who did not gain weight (and lost weight on average). In a multiple linear regression (Table 3), changes in weight and glucose were significantly

Table 2—*Risk factors for impaired glucose tolerance: multivariate analysis by weight-change categories*

	Subject groups			
	No weight gain (80/387)*		Weight gain (295/1026)*	
Variables†	Hazard rate ratio (95% CI)	*P* value	Hazard rate ratio (95% CI)	*P* value
Adjusted for age and sex				
BMI (5 kg/m^2)	1.13 (0.97–1.30)	0.11	1.28 (1.18–1.39)	<0.001
Fasting insulin	1.44 (1.12–1.85)	0.004	1.72 (1.50–1.97)	<0.001
2-h insulin	1.15 (0.92–1.44)	0.20	1.58 (1.40–1.78)	<0.001
Adjusted for age, sex, BMI, 2-h glucose				
Fasting insulin	1.37 (1.03–2.42)	0.03	1.44 (1.23–1.68)	<0.001
2-h insulin	0.92 (0.71–1.22)	0.59	1.20 (1.02–1.42)	0.03

*Subjects who developed IGT/Total number of subjects.
†For each variable, the hazard rate ratio and 95% CI are given for a difference at baseline corresponding to a doubling (insulin concentrations) or to the number in parentheses (BMI).

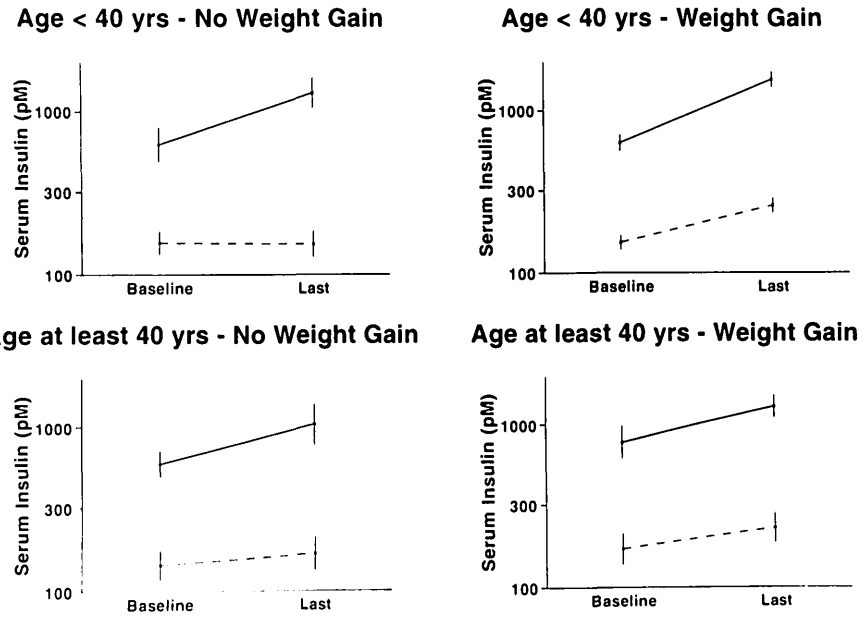

Figure 1—*Changes in fasting (– – –) and 2-h (——) insulin concentrations between the baseline and the last follow-up examination in subjects who developed IGT with or without weight gain, according to baseline age (<40 yr of age or ≥40 yr of age). Means with upper and lower 95% CIs for the mean are plotted on a logarithmic scale.*

and independently associated with change in fasting serum insulin concentrations. In contrast, change in weight was not related to change in 2-h insulin concentrations. Older age was associated with a smaller increase in 2-h insulin concentration, for a given increase in 2-h glucose concentration.

Body fat distribution

We measured waist-to-thigh ratio for a subset of the subjects at the follow-up examination. Age- and sex-adjusted waist-to-thigh ratios were higher in patients with IGT than in those with NGT, both in the group that did gain weight (NGT: 1.62; IGT: 1.72, $P < 0.001$, $n = 489$) and in the group that did not gain weight (NGT: 1.61; IGT: 1.80, $P < 0.001$, $n = 90$). The ratios were not statistically different in the two groups with IGT, despite a significantly greater age- and sex-adjusted BMI in the subjects who gained weight (weight-gain group: 35.7 kg/m^2; no weight-gain group: 30.1 kg/m^2, $P < 0.001$).

CONCLUSIONS— Glucose tolerance can deteriorate even in the absence of weight gain. A higher baseline fasting insulin concentration is associated with the subsequent development of IGT regardless of weight change. Fasting insulin concentrations in nondiabetic Pima Indians are positively correlated with measures of insulin resistance (5). The fasting hyperinsulinemia of subjects at risk for developing IGT is not likely to be explained by a higher proportion of proinsulin, because this proportion has been shown to be similar in Pima Indians with NGT and IGT (6). Thus, in Pima Indians, insulin resistance is the main reason for a high fasting insulin concentration.

Even in subjects with stable weight, insulin concentrations increased with the development of IGT as shown in the multiple regression model (Table 3). Thus, weight gain appears to be a contributing, but not a necessary, factor in the development of IGT. Body fat distribution, however, might be of more importance, because the subjects with IGT had a more central obesity than those with NGT, regardless of weight change.

Older age (7) and physical inactivity (8), both of which are associated with a decrease in insulin sensitivity, are other factors potentially involved in the changes in insulin concentrations associated with IGT.

In summary, this study is in agreement with the hypothesis (2) that IGT develops in Pima Indians with preexisting insulin resistance. IGT seems to

Table 3—*Prediction of serum insulin changes with the development of IGT, as a function of plasma glucose and weight changes by multiple linear regression*

	Fasting insulin change*			2-h Insulin change*		
	β†	SE‡	*P*	β†	SE‡	*P*
Variables						
Intercept	−0.015	0.167		0.345	0.200	
Female sex	0.051	0.090	0.57	0.001	0.096	0.99
Follow-up mean (yr)	0.048	0.018	<0.001	0.060	0.019	0.002
Baseline age (yr)	−0.002	0.003	0.45	−0.010	0.003	0.005
Weight change (kg)	0.013	0.005	0.009	0.004	0.005	0.45
Plasma glucose change (mM)§	0.271	0.065	<0.001	0.173	0.034	<0.001

*Dependent variable is the natural logarithm of the ratio of final to baseline insulin.
†Coefficient in the multiple linear regression equation.
‡SE of the coefficient.
§FPG in the regression of fasting serum insulin changes, 2-h plasma glucose in the regression of 2-h serum insulin changes.

occur when the β-cells need to respond to an additional demand for insulin secretion. Weight gain is the most common precipitating factor. Aging and physical inactivity are other important possible precipitating factors.

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