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Evaluation of Simple Indices of Insulin Sensitivity and Insulin Secretion for Use in Epidemiologic Studies

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The metabolic characteristics of type 2 diabetes, insulin resistance, and diminished insulin secretion are costly to measure directly. To evaluate the utility of several simple indices derived from insulin and glucose measurements, the indices were examined from 1982 to 1997 with respect to correlation with more sophisticated measures of insulin sensitivity and secretion in Pima Indians in the Gila River Indian Community of Arizona. Ability to predict the incidence of diabetes in 1,731 persons was also examined. Indices were calculated from fasting and 2-hour glucose (G_0, G_{120}) and insulin (I_0, I_{120}) concentrations obtained during an oral glucose tolerance test. Fasting serum insulin concentration and the insulin sensitivity index ($10^4/(I_0 \times G_0)$) each showed a moderate correlation with the estimate of insulin sensitivity derived from the hyperinsulinemic-euglycemic clamp ($|r| \approx 0.60$). They also strongly predicted the incidence of diabetes (incidence rate ratio comparing the most and least insulin-resistant tertile groups ≈ 3.0). Corrected insulin response ($I_{120}/(G_{120} \times (G_{120} - 70))$) was modestly correlated with insulin secretion as measured by an intravenous glucose tolerance test ($r = 0.35$). Impaired insulin secretion assessed by this index predicted incidence of diabetes, particularly after control for insulin sensitivity index (incidence rate ratio = 1.6). Thus, simple indices of insulin sensitivity and secretion may be reasonable surrogates for more sophisticated measures in epidemiologic studies. *Am J Epidemiol* 2000;151:190–8.

diabetes mellitus, non-insulin-dependent; epidemiologic studies; incidence; insulin resistance

Type 2 diabetes mellitus is characterized by both diminished insulin sensitivity and deficient insulin secretion; these metabolic parameters are important, potentially genetically determined precursors of diabetes (1, 2). Insulin sensitivity and secretion can be measured by the hyperinsulinemic-euglycemic "clamp" and the insulin response to an intravenous glucose infusion. In nondiabetic subjects, these measures strongly predict the subsequent incidence of diabetes (3) and are often considered the "gold standards" for assessment of insulin sensitivity and secretion. However, as these measures are labor intensive, they are difficult to obtain in the large numbers of persons typically required for epidemiologic investigations. In such studies, simple indices derived from more easily measured parameters, for example, during an oral glucose tolerance test, would be useful. Several such indices have been proposed (4–7), but their utility in epidemiologic studies of diabetes depends on the extent to which they correlate with more sophisticated measures and on whether they predict the incidence of diabetes in a fashion similar to the more sophisticated measures.

Since 1965, the Pima Indians of the Gila River Indian Community in central Arizona have participated in a population-based longitudinal epidemiologic study of diabetes (8, 9); since 1982, a subset of this population has participated in detailed physiologic studies of insulin sensitivity and secretion (3, 10). The present study of Pima Indians examined simple indices of insulin sensitivity and secretion with respect to their association with more sophisticated measures and their ability to predict the incidence of diabetes.

MATERIALS AND METHODS

Subjects

Since 1965, a longitudinal epidemiologic study of diabetes has been conducted in the Gila River Indian

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Abbreviations: AIR_{glue}, acute insulin response to intravenous glucose; CIR_x, corrected insulin response, measured x minutes after an oral glucose load (other x abbreviations defined similarly); G_x, plasma glucose concentration; HOMA-βC, estimate of β-cell function from the homeostatic model; HOMA-IR, estimate of insulin resistance from the homeostatic model; I_x, serum insulin concentration; IRR, incidence rate ratio; ISI_x, insulin sensitivity index; M_{130}, estimate of insulin sensitivity from hyperinsulinemic-euglycemic clamp at an insulin concentration of 130 μU/ml.

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Community of central Arizona (8). Most of the residents of this community are Pima or Tohono O'odham Indians, and the prevalence of type 2 diabetes is extraordinarily high (8, 9). Every 2 years, all community members aged ≥5 years are invited to have a health examination that includes a 75 g oral glucose tolerance test.

Plasma glucose and serum insulin concentrations are measured in specimens obtained when subjects are fasting and 2 hours after the oral glucose load. World Health Organization criteria for epidemiologic studies are used to classify subjects as having diabetes (2-hour postload plasma glucose concentration ≥11.1 mM) or impaired glucose tolerance (7.8 mM ≤ 2-hour plasma glucose concentration < 11.1 mM) (11). Diagnostic criteria based solely on fasting plasma glucose concentration have been proposed recently (12), and generally similar results were obtained when these criteria were used. For comparison with previous studies, the present results are reported with subjects classified by 2-hour plasma glucose concentration.

Two different insulin radioimmunoassays were used: a modified Herbert-Lau assay (13) from 1973 to 1986 and a Concept 4 analyzer since 1987 (ICN Pharmaceuticals, Inc., Costa Mesa, California). To account for differences in these assays, variables were standardized within assay for statistical analyses, as described below. Height and weight measured with subjects wearing light clothing and no shoes were used to calculate body mass index (kg/m^2). The present analyses involved persons of full Native American heritage who were at least 20 years of age.

Simple indices

A number of indices of insulin sensitivity and secretion were evaluated. They were calculated from the fasting and 2-hour plasma glucose levels (G_0, G_{120}) and the fasting and 2-hour serum insulin levels (I_0, I_{120}). For subjects who have participated in detailed physiologic studies, 30-minute levels have also been determined; indices based on these measures (G_{30}, I_{30}) were examined in this subset. Both I_0 and I_{120} can be used as simple measures of insulin resistance (4), and the ratio of postload to fasting insulin has been proposed as a measure of insulin secretion (14). Sluiter et al. have proposed a mathematical model for calculating an insulin sensitivity index (ISI) and a corrected insulin response (CIR) to assess insulin secretion, although the CIR can be calculated only for time points after the oral glucose load has been administered (5, 6). The homeostatic model allows for estimates of insulin resistance (HOMA-IR) and β-cell function (HOMA-βC) derived from I_0 and G_0 (7); since the HOMA-IR estimate is equivalent to the reciprocal of ISI_0, the present study reports results for ISI_0 only. The ratio of insulin to glucose concentrations has been used as a measure of both insulin resistance (for fasting values) and insulin secretion (for postload values) (15–17). The insulinogenic index, the ratio of the increment in insulin concentration to the increment in glucose concentration (ΔI/ΔG), has also been proposed as a measure of insulin secretion (17, 18). Formulae for the indices are given in table 1.

For statistical analyses, natural logarithms of the indices were used to reduce skewness. To account for sex differences and differences between insulin assays, all variables were standardized by sex and assay to a mean of 0 and a standard deviation of 1.

Correlations with more sophisticated measures

The extent to which these indices correlate with more sophisticated measures of insulin sensitivity and insulin secretion was examined in 469 nondiabetic subjects who had participated in the metabolic studies. In these studies, a hyperinsulinemic-euglycemic clamp with insulin infused to achieve physiologic levels of hyperinsulinemia (130 μU/ml) has been used to evaluate insulin sensitivity (M_{130}) (refer to Lillioja et al. (10) for further details). The first phase of insulin secretion is measured as the acute insulin response above the basal level (AIR_{gluc}), determined 3–5 minutes after administration of a 25 g intravenous glucose bolus (19). Simple indices of insulin resistance and secretion were calculated from an oral glucose tolerance test obtained during the same inpatient visit at which M_{130} and AIR_{gluc} were measured (i.e., within 15 days). The association of each of the simple indices with M_{130} and AIR_{gluc} was described by the correlation coefficient. Since the degree to which these indices accurately reflect the underlying physiology may depend on the degree of glucose intolerance, separate analyses were conducted for subjects with impaired glucose tolerance and for those with normal glucose tolerance.

Analyses of diabetes incidence

Analyses of the incidence of diabetes were conducted for 1,731 participants in the longitudinal epidemiologic study who were nondiabetic and at least 20 years of age at baseline. Included were 1,067 women and 664 men whose mean age at baseline was 31 (standard deviation, 12) years. Subjects were followed until they developed diabetes or until their last examination, whichever occurred first.

Incidence of diabetes was calculated as events per 1,000 person-years by tertile groups of the indices of insulin sensitivity and secretion at the baseline examina-

TABLE 1. Correlations of indices of insulin sensitivity and secretion with estimates of insulin sensitivity derived from the hyperinsulinemic-euglycemic clamp (M_{130}) and of insulin secretion measured by the acute insulin response to intravenous glucose (AIR_{gluc}), Gila River Indian Community, Arizona, 1982–1997

Index (abbreviation)	Formula†	NGT‡		IGT‡		NGT + IGT	
		M_{130} (n = 274)	AIR_{gluc} (n = 245)	M_{130} (n = 183)	AIR_{gluc} (n = 153)	M_{130} (n = 457)	AIR_{gluc} (n = 398)
Indices based exclusively on fasting insulin and glucose concentrations							
Fasting insulin (I_0)	I_0	−0.57**	0.30**	−0.56**	−0.05	−0.60**	0.11*
Insulin sensitivity index (ISI_0)§	$10^4/(I_0 \times G_0)$	0.59**	−0.29**	0.56**	0.12	0.62**	−0.07
Insulin/glucose ratio (I_0/G_0)	I_0/G_0	−0.54**	0.31**	−0.54**	0.02	−0.56**	0.15**
HOMA β-cell function (HOMA-βC)¶	$(20 \times I_0)/(G_0 - 3.5)$	−0.35**	0.29**	−0.43**	0.16*	−0.37**	0.23**
Indices including 30-minute insulin and glucose concentrations							
30-minute insulin (I_{30})	I_{30}	−0.36**	0.43**	−0.26**	0.45**	−0.29**	0.43**
Insulin sensitivity index (ISI_{30})§	$10^4/(I_{30} \times G_{30})$	0.38**	−0.36**	0.28**	−0.35**	0.34**	−0.33**
Insulin/glucose ratio (I_{30}/G_{30})	I_{30}/G_{30}	−0.32**	0.49**	−0.23**	0.54**	−0.23**	0.51**
Insulin ratio (I_{30}/I_0)	I_{30}/I_0	0.29**	0.11	0.29**	0.53**	0.36**	0.31**
Insulinogenic index ($\Delta I_{30}/\Delta G_{30}$)#	$(I_{30} - I_0)/(G_{30} - G_0)$	−0.21**	0.49**	−0.18*	0.58**	−0.13**	0.54**
Corrected insulin response (CIR_{30})††	$I_{30}/(G_{30} \times (G_{30} - 70))$	−0.15*	0.52**	−0.13	0.61**	−0.05	0.58**
Indices including 2-hour insulin and glucose concentrations							
2-hour insulin (I_{120})	I_{120}	−0.53**	0.21**	−0.43**	0.30**	−0.56**	0.12*
Insulin sensitivity index (ISI_{120})§	$10^4/(I_{120} \times G_{120})$	0.52**	−0.16*	0.46**	−0.26**	0.57**	−0.04
Insulin/glucose ratio (I_{120}/G_{120})	I_{120}/G_{120}	−0.51**	0.26**	−0.39**	0.33**	−0.50**	0.22**
Insulin ratio (I_{120}/I_0)	I_{120}/I_0	−0.01	−0.08	0.08	0.41**	−0.06	0.04
Insulinogenic index ($\Delta I_{120}/\Delta G_{120}$)#	$(I_{120} - I_0)/(G_{120} - G_0)$	−0.30**	0.23**	−0.26**	0.29**	−0.22**	0.27**
Corrected insulin response (CIR_{120})††	$I_{120}/(G_{120} \times (G_{120} - 70))$	−0.30**	0.26**	−0.30**	0.37**	−0.17**	0.36**

* $p < 0.05$; ** $p < 0.01$.

† I_x, serum insulin concentration measured x minutes after an oral glucose load; G_x, plasma glucose concentration measured x minutes after an oral glucose load.

‡ NGT, normal glucose tolerance; IGT, impaired glucose tolerance.

§ Refer to Sluiter et al. (6).

¶ β-cell function estimated by the homeostatic (HOMA) model; value defined only if $G_0 > 3.5$ mM; units for G_0 are expressed in mM; refer to Matthews et al. (7).

Value defined only if $I_x > I_0$ and $G_x > G_0$.

†† Units for G_0 are expressed in mg/dl; value defined only if $G_x > 70$ mg/dl (3.9 mM) and $G_x > G_0$; refer to Sluiter et al. (5).

tion and by decades of age; when a subject moved from one age stratum to the next, person-years were apportioned accordingly. Poisson regression analysis was used to calculate the incidence rate ratio comparing one tertile group with another, adjusted for age and sex (20). For simplicity of presentation, tertile groups were categorized as at "low risk," "medium risk," or "high risk" for diabetes on the basis of the expected degree of insulin sensitivity (I_0, ISI_0, I_0/G_0, I_{120}, ISI_{120}) or insulin secretion (HOMA-βC, I_{120}/I_0, I_{120}/G_{120}, $\Delta I_{120}/\Delta G_{120}$, CIR_{120}); the group hypothetically at low risk for diabetes was considered the reference group (i.e., those who were putatively the most insulin sensitive or who had the greatest insulin secretion). As obesity is a strong risk factor for type 2 diabetes (21) and is strongly correlated with insulin resistance (22, 23), tertiles of body mass index were included as covariates in some analyses. Separate analyses stratified by whether subjects had normal (n = 1,382) or impaired (n = 349) glucose tolerance at baseline were conducted, since metabolic determinants of diabetes may vary in these groups.

The predictive ability of indices based on 30-minute postload values could be assessed for only the subset of subjects who had participated in the detailed physiologic studies, since these measurements have not been made routinely in the longitudinal study. Therefore, a similar analysis was undertaken of the 249 subjects who had participated in these studies and who also had undergone at least one subsequent examination in the longitudinal population study. This analysis included 121 women and 128 men whose mean age at baseline was 29 (standard deviation, 6) years.

RESULTS

Correlations with M_{130} and AIR_{gluc}

The correlations of these indices of insulin sensitivity and secretion with M_{130} and AIR_{gluc} are shown in

table 1. For all subjects, the magnitude of the correlations of the indices of insulin sensitivity based on fasting and 2-hour postload measurements (I_0 I_0/G_0, ISI_0, I_{120}, ISI_{120}) with M_{130} was similar. The correlations of I_{120} and ISI_{120} with M_{130} were somewhat lower for subjects with impaired glucose tolerance than for those with normal glucose tolerance, while correlations of the indices based on fasting insulin concentrations (I_0, ISI_0, I_0/G_0) with M_{130} were similar for subjects with normal glucose tolerance and impaired glucose tolerance.

The indices of insulin secretion (HOMA-βC, I_{30}, I_{30}/I_0, I_{30}/G_{30}, $\Delta I_{30}/\Delta G_{30}$, CIR_{30}, I_{120}/I_0, I_{120}/G_{120}, $\Delta I_{120}/\Delta G_{120}$, CIR_{120}) showed significant but generally modest correlations with AIR_{gluc}. The ratio measures of postload to fasting insulin levels were significantly correlated with AIR_{gluc} only in those subjects with impaired glucose tolerance, while the remaining indices were correlated significantly with AIR_{gluc} in subjects with either normal or impaired glucose tolerance. For indices based on the 30-minute values, the correlation with AIR_{gluc} was higher than for indices based on the 2-hour values, and the CIR tended to be more strongly correlated than the other indices. In fact, CIR_{30} was the only index whose correlation with AIR_{gluc} was consistently higher than 0.5. The correlations of G_0 with M_{130} and AIR_{gluc} (–0.42 and –0.20, respectively) were similar to those of G_{120} with the same variables (–0.42 and –0.22, respectively).

Incidence of diabetes

Analyses of the incidence of diabetes showed that 591 subjects developed diabetes in a median follow-up time of 8.9 (range, 0.1–24.7) years. Age-adjusted incidence rate ratios comparing the incidence of diabetes in tertile groups defined by indices of insulin sensitivity and secretion are shown in table 2. For all subjects and for those with normal glucose tolerance at baseline, indices of insulin sensitivity were strongly associated with the incidence of diabetes; for subjects in the most insulin-resistant groups, the incidence was about three times higher than for those in the most insulin-sensitive groups. After adjustment for body mass index, the incidence rate ratios were lower, but the associations of insulin resistance with diabetes incidence were still substantial. Among subjects with impaired glucose tolerance at baseline, the relation between diabetes incidence and these indices of insulin sensitivity was much weaker, and there were no statistically significant associations.

Among the indices of insulin secretion, HOMA-βC and I_{120}/G_{120} were significantly associated with the incidence of diabetes in subjects with normal glucose tolerance at baseline. However, since those who were hypothetically at low risk had the highest incidence of diabetes, these associations did not appear to be due to the ability of the indices to assess insulin secretion. Among subjects with impaired glucose tolerance at baseline, those with greater insulin secretory dysfunction, as determined by either I_{120}/I_0 or CIR_{120}, had a significantly higher incidence of diabetes than those with less insulin secretory dysfunction. Among all subjects, HOMA-βC, I_{120}/G_{120}, $\Delta I_{120}/\Delta G_{120}$, and CIR_{120} were significantly associated with the incidence of diabetes; the associations with $\Delta I_{120}/\Delta G_{120}$ and CIR_{120} were U-shaped, and those with HOMA-βC and I_{120}/G_{120} were again such that the highest incidence was evident among those who were hypothetically at low risk for diabetes.

The association of diabetes incidence with insulin secretory dysfunction, as defined by CIR_{120}, was more apparent when ISI_0 was taken into account (figure 1). Subjects with the highest level of impaired insulin secretion, as determined by CIR_{120}, had a higher incidence of diabetes than those with the lowest level of insulin secretory dysfunction, after control for age and ISI_0 (incidence rate ratio (IRR) = 1.6, $p < 0.01$). Similarly, after control for CIR_{120}, ISI_0 was associated with the incidence of diabetes (IRR = 3.5, $p < 0.01$).

Among the 249 participants in the detailed physiologic studies for whom longitudinal data were also available, 64 subsequently developed diabetes in a median of 4.5 (range, 0.1–15.5) years. Incidence rate ratios for tertile groups defined by the three best simple indices of insulin secretion (I_{30}/G_{30}, $\Delta I_{30}/\Delta G_{30}$, and CIR_{30}) and, for comparison, ISI_0 are shown in table 3. Insulin resistance, as assessed by ISI_0, was strongly associated with the incidence of diabetes. Impaired insulin secretion, assessed by $\Delta I_{30}/\Delta G_{30}$ or CIR_{30}, was modestly associated with the incidence of diabetes, and this association strengthened after adjustment for body mass index. When I_{30}/G_{30} was used to estimate insulin secretion, little association was found with the incidence of diabetes. By contrast, AIR_{gluc} and M_{130} were more strongly associated with diabetes incidence than were any of the simpler indices (for each, p for trend < 0.01).

Diabetes incidence rates stratified by both $\Delta I_{30}/\Delta G_{30}$ and ISI_0 and by CIR_{30} and ISI_0 are shown in figure 2. After control for ISI_0, insulin secretory dysfunction, as defined by $\Delta I_{30}/\Delta G_{30}$, was significantly associated with diabetes incidence (comparison of the high- and low-risk tertile groups: IRR = 2.8, p for trend < 0.01). Likewise, insulin resistance, as defined by ISI_0, strongly predicted subsequent diabetes after control for $\Delta I_{30}/\Delta G_{30}$ (IRR = 6.8, p for trend < 0.01). Similarly, after control for ISI_0, CIR_{30} was associated with the incidence of diabetes (IRR = 2.4, p for trend

TABLE 2. Incidence rate ratios for tertile groups of indices of insulin resistance and insulin secretory dysfunction, Gila River Indian Community, Arizona, 1973–1998

Index*	Adjusted for age				Adjusted for age and body mass index			
	Low risk†	Medium risk†	High risk†	*p* value‡	Low risk†	Medium risk†	High risk†	*p* value‡
Subjects with normal glucose tolerance								
I_0§	1.0	1.7	3.0	<0.01	1.0	1.4	2.2	<0.01
ISI_0¶	1.0	1.8	3.2	<0.01	1.0	1.5	2.4	<0.01
I_0/G_0§	1.0	1.7	2.7	<0.01	1.0	1.5	1.9	<0.01
I_{120}§	1.0	2.0	2.8	<0.01	1.0	1.8	2.2	<0.01
ISI_{120}¶	1.0	2.0	2.8	<0.01	1.0	1.7	2.1	<0.01
I_{120}/G_{120}#	1.0	0.7	0.4	<0.01	1.0	0.8	0.5	<0.01
I_{120}/I_0#	1.0	1.2	1.0	0.36	1.0	1.0	0.9	0.70
$\Delta I_{120}/\Delta G_{120}$#	1.0	0.8	0.8	0.09	1.0	0.8	0.9	0.31
HOMA-βC#	1.0	0.8	0.5	<0.01	1.0	0.9	0.6	<0.01
CIR_{120}#	1.0	0.8	0.8	0.08	1.0	0.8	0.9	0.26
Subjects with impaired glucose tolerance								
I_0§	1.0	1.3	1.3	0.22	1.0	1.1	1.1	0.85
ISI_0¶	1.0	1.3	1.5	0.09	1.0	1.1	1.2	0.58
I_0/G_0§	1.0	1.4	1.5	0.04	1.0	1.3	1.3	0.32
I_{120}§	1.0	1.0	0.9	0.94	1.0	0.9	0.8	0.61
ISI_{120}¶	1.0	1.0	1.1	0.71	1.0	1.0	1.0	0.98
I_{120}/G_{120}#	1.0	0.9	1.2	0.23	1.0	1.1	1.4	0.10
I_{120}/I_0#	1.0	1.6	1.9	<0.01	1.0	1.5	1.8	0.01
$\Delta I_{120}/\Delta G_{120}$#	1.0	1.1	1.2	0.64	1.0	1.2	1.3	0.24
HOMA-βC#	1.0	0.8	0.9	0.53	1.0	0.9	1.0	0.71
CIR_{120}#	1.0	1.0	1.5	0.02	1.0	1.1	1.7	0.01
Subjects with normal or impaired glucose tolerance								
I_0§	1.0	2.0	3.2	<0.01	1.0	1.7	2.4	<0.01
ISI_0¶	1.0	2.1	3.6	<0.01	1.0	1.8	2.8	<0.01
I_0/G_0§	1.0	1.8	2.6	<0.01	1.0	1.5	1.9	<0.01
I_{120}§	1.0	2.0	2.9	<0.01	1.0	1.7	2.3	<0.01
ISI_{120}¶	1.0	1.9	3.3	<0.01	1.0	1.7	2.6	<0.01
I_{120}/G_{120}#	1.0	0.8	0.5	<0.01	1.0	0.9	0.6	<0.01
I_{120}/I_0#	1.0	1.0	0.9	0.48	1.0	0.9	0.9	0.39
$\Delta I_{120}/\Delta G_{120}$#	1.0	0.9	1.2	0.08	1.0	0.9	1.3	<0.01
HOMA-βC#	1.0	0.8	0.5	<0.01	1.0	0.9	0.7	0.01
CIR_{120}#	1.0	0.8	1.2	<0.01	1.0	0.8	1.3	<0.01

* I_0, fasting serum insulin concentration; ISI_0, fasting insulin sensitivity index; I_0/G_0, fasting insulin-glucose ratio; I_{120}, 2-hour serum insulin concentration; ISI_{120}, 2-hour insulin sensitivity index; I_{120}/G_{120}, 2-hour insulin-glucose ratio;$\Delta I_{120}/\Delta G_{120}$, 2-hour insulinogenic index; I_{120}/I_0, 2-hour fasting insulin ratio; HOMA-βC, β-cell function by the homeostatic model; CIR_{120}, 2-hour corrected insulin response.

† Tertile groups of subjects were categorized as being hypothetically at low, medium, or high risk for diabetes on the basis of the expected degree of insulin sensitivity or secretion. Incidence rate ratios were calculated comparing the incidence of the higher risk groups with that of the low-risk group by using Poisson regression. The rate ratio for the low-risk tertile is thus 1.0 by definition; rate ratios for the remaining groups of >1 suggest that the index appropriately defines the risk for diabetes.

‡ Calculated by using the likelihood ratio test (2 degrees of freedom).

§ Lower values are considered to represent greater insulin sensitivity (I_0, I_{120}, I_0/G_0).

¶ Higher values are considered to represent greater insulin sensitivity (ISI_0, ISI_{120}).

Higher values are considered to represent greater insulin secretion (I_{120}/G_{120}, I_{120}/I_0, $\Delta I_{120}/\Delta G_{120}$, HOMA-$\beta$C, CIR_{120}).

< 0.01), and ISI_0 strongly predicted diabetes incidence after adjustment for CIR_{30} (IRR = 6.2, p for trend < 0.01). For AIR_{gluc} and M_{130}, the corresponding incidence rate ratios were 4.8 and 3.4, respectively (for each, p for trend < 0.01).

DISCUSSION

Associations with M_{130} and AIR_{gluc}

Simple indices of insulin sensitivity and insulin secretion would be very useful in epidemiologic and

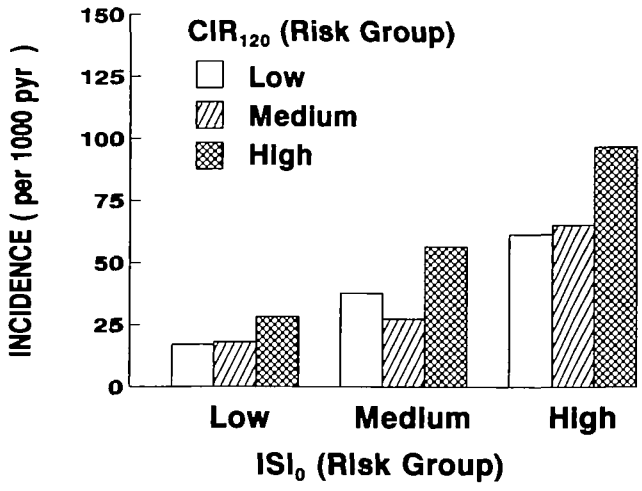

FIGURE 1. Age-adjusted incidence of diabetes in tertile groups defined by fasting insulin sensitivity index (ISI_0) and by 2-hour corrected insulin response (CIR_{120}), Gila River Indian Community, Arizona, 1973–1998. Tertiles were categorized as being at "low," "medium," or "high" risk for diabetes on the basis of the expected degree of insulin sensitivity (ISI_0) or insulin secretion (CIR_{120}). Incidence rates per 1,000 person-years (pyr) were calculated from the coefficients of a Poisson regression model for subjects aged 30–39 years.

genetic studies. The utility of such indices depends in part on how well they correlate with more accurate measures. The present analyses showed that serum insulin concentrations, measured during fasting and 2 hours after administration of an oral glucose load, were moderately correlated (about –0.60) with the estimate of insulin sensitivity derived from the hyperinsulinemic-euglycemic clamp. Incorporating additional information from the fasting plasma glucose concentration into the index of insulin sensitivity (ISI_0 or, equivalently, HOMA-IR) marginally improved this correlation. Given that both I_0 and G_0 were negatively correlated with insulin sensitivity, it is not surprising that insulin sensitivity was more strongly correlated with their product (HOMA-IR or its reciprocal, ISI_0) than with their ratio.

For subjects with normal glucose tolerance, the results of the present study were similar to those observed in Finns (4), in English subjects (17), and in the Insulin Resistance Atherosclerosis Study (24). In all of these studies, however, the correlations were lower for subjects with impaired glucose tolerance; in the present analysis, there was little difference between those with normal and those with impaired glucose tolerance regarding the association of the indices based on fasting insulin with M_{130}. These differences could reflect differences in biologic characteristics of Pima Indians with impaired glucose tolerance compared with other populations. However, as assessed by the method of Fisher (25), there were no statistically significant differences between the correlations observed in the present study and those observed in any of these smaller studies. Therefore, the differences between studies could be due to chance.

Correlations for most of the indices of insulin secretion with the estimate derived from the insulin response to intravenous glucose were more modest, but they generally were stronger for indices derived from the 30-minute postload insulin and glucose concentrations than for those derived from 2-hour or fasting measurements. For CIR_{30}, the correlation with AIR_{gluc} was similar in magnitude to that between the insulin resistance indices and M_{130} ($r = 0.58$), but the correlations of AIR_{gluc} with I_{30}/G_{30} and $\Delta I_{30}/\Delta G_{30}$ were only slightly lower. The correlations of AIR_{gluc} with $\Delta I_{30}/\Delta G_{30}$ were not significantly different from those

TABLE 3. Incidence rate ratios for tertile groups of indices of insulin secretion for a subset of 249 subjects for whom detailed metabolic studies* were available, Gila River Indian Community, Arizona, 1982–1998

Index†	Adjusted for age				Adjusted for age and body mass index			
	Low risk‡	Medium risk‡	High risk‡	*p* for trend	Low risk‡	Medium risk‡	High risk‡	*p* for trend
ISI_0	1.0	2.0	4.8	<0.01	1.0	1.4	2.9	0.01
I_{30}/G_{30}	1.0	0.6	0.7	0.19	1.0	0.8	1.1	0.90
$\Delta I_{30}/\Delta G_{30}$	1.0	1.3	1.6	0.15	1.0	2.1	2.6	<0.01
CIR_{30}	1.0	1.3	1.4	0.23	1.0	1.9	2.3	0.01

* These subjects had either normal or impaired glucose tolerance at baseline.

† ISI_0, fasting insulin sensitivity index; I_{30}/G_{30}, 30-minute insulin-glucose ratio; $\Delta I_{30}/\Delta G_{30}$, 30-minute insulinogenic index; CIR_{30}, 30-minute corrected insulin response.

‡ Tertile groups of subjects were categorized as being hypothetically at low, medium, or high risk for diabetes on the basis of the expected degree of insulin sensitivity or secretion. Incidence rate ratios were calculated comparing the incidence of the higher risk groups with that of the low-risk group by using Poisson regression. The rate ratio for the low-risk tertile is thus 1.0 by definition; rate ratios for the remaining groups of >1 suggest that the index appropriately defines the risk for diabetes.

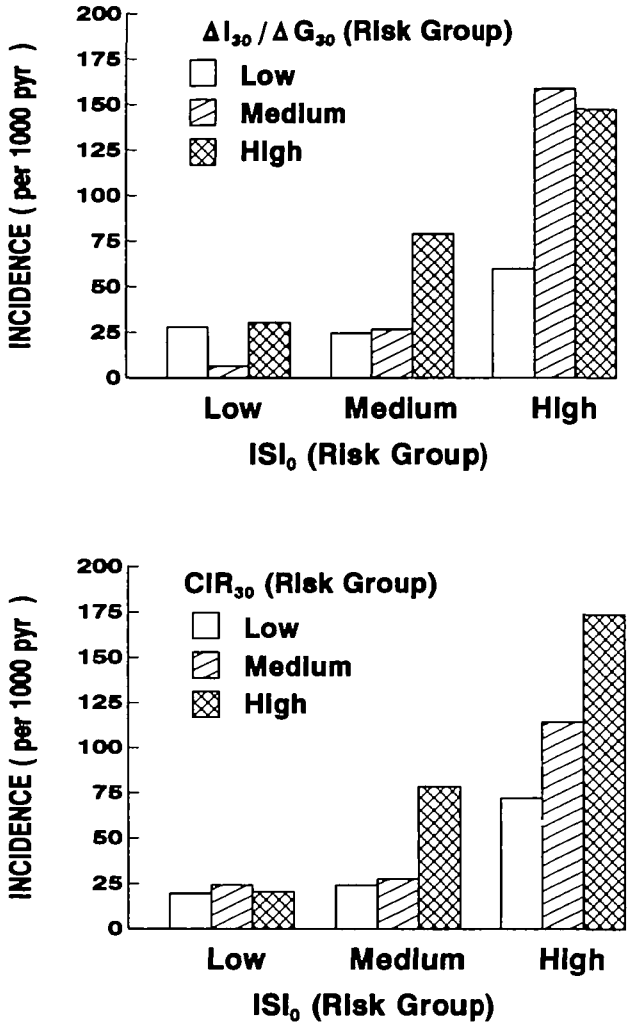

FIGURE 2. Age-adjusted incidence of diabetes in tertile groups defined by fasting insulin sensitivity index (ISI_0) and by 30-minute insulinogenic index ($\Delta I_{30}/\Delta G_{30}$, top panel) or corrected insulin response (CIR_{30}, bottom panel) in 249 subjects who participated in detailed metabolic studies, Gila River Indian Community, Arizona, 1982–1998. Tertiles were categorized as being at "low," "medium," or "high" risk for diabetes on the basis of the expected degree of insulin sensitivity (ISI_0) or insulin secretion ($\Delta I_{30}/\Delta G_{30}$, CIR_{30}). Incidence rates per 1,000 person-years (pyr) were calculated from the coefficients of a Poisson regression model for subjects aged 30–39 years.

observed in an English population (17). Although the HOMA-βC index was derived to produce a measure of insulin secretion that is in theory independent of insulin resistance (7), in the present data its correlation with M_{130} was stronger than that with AIR_{gluc}.

It has been suggested that hyperinsulinemia that occurs 2 hours after an oral glucose load in persons with impaired glucose tolerance may reflect impaired early insulin release—with a compensatory response to the resultant hyperglycemia—more than insulin resistance (26). The correlations of I_{120} and related indices with M_{130} were slightly lower in persons with impaired versus normal glucose tolerance, while the correlations with AIR_{gluc} were slightly higher. However, the interaction appeared to be relatively modest. It has also been suggested that the 2-hour glucose concentration is influenced primarily by insulin sensitivity, while the fasting glucose concentration is influenced primarily by insulin secretion (27). In this population, however, both fasting and 2-hour glucose values were more strongly correlated with M_{130} than with AIR_{gluc}. In the present study, it was assumed that M_{130} and AIR_{gluc} represented the "gold standards" for assessing insulin sensitivity and secretion. While these methods have been used widely, alternate methods such as the hyperglycemic "clamp" may be superior, particularly for assessing insulin secretion (28).

Implications for epidemiologic studies

These simple indices may be useful estimates of insulin sensitivity and insulin secretion in epidemiologic studies of diabetes and related conditions, despite their relatively modest correlations with more accurate measures. The present analyses, in which I_0 or ISI_0 was used to assess insulin sensitivity and $\Delta I_{30}/\Delta G_{30}$, CIR_{30}, or CIR_{120} was used to assess insulin secretion, suggest that both insulin resistance and insulin secretory dysfunction predict diabetes in Pima Indians. This finding is consistent with analyses in which M_{130} and AIR_{gluc} are used, both of which strongly predict diabetes (3). The fact that the present results are qualitatively similar to those in which the more sophisticated measures are used suggests that these simple indices may be useful in epidemiologic studies in which it would be difficult to perform the more sophisticated measurements. One might expect the association of simple indices with a disease influenced by insulin resistance or insulin secretory dysfunction to be attenuated relative to the associations with more sophisticated measures. Such a phenomenon has been observed for the association of cardiovascular risk factors with insulin resistance (29). The present analyses showed a strong association of insulin sensitivity indices with diabetes incidence, while the association with insulin secretion assessed by $\Delta I_{30}/\Delta G_{30}$ or CIR_{30} was more modest. This finding suggests that use of these indices may result in a greater underestimation of the effect of insulin secretion than of insulin resistance. The further attenuation of the association of insulin secretion, as assessed by CIR_{120}, with diabetes incidence probably reflects the lower correlation of this index with AIR_{gluc}.

As greater insulin secretion is necessary to produce an equivalent level of glycemia in the face of greater insulin resistance, it is important to account for both variables simultaneously to avoid underestimating the effect of pancreatic β-cell dysfunction (30, 31). When

$\Delta I_{30}/\Delta G_{30}$, CIR_{30}, or CIR_{120} was analyzed simultaneously with ISI_0, the effect of insulin secretory dysfunction as assessed by these indices was more apparent. Compared with the incidence rate ratios observed by using M_{130} and AIR_{gluc}, the effect of insulin resistance was overestimated while that of impaired insulin secretion was underestimated. Thus, although these simple indices may be useful for determining whether a disease is associated with insulin resistance or impaired insulin secretion, it may be difficult to assess the importance of each factor relative to the other.

The present analyses also show that the indices of insulin sensitivity were strongly associated with the incidence of diabetes among subjects with normal glucose tolerance at baseline, while the effect of indices of insulin secretion (CIR_{120} and I_{120}/I_0) was most apparent among those with impaired glucose tolerance. This finding is consistent with the hypothesis, suggested by previous analyses of Pima Indians, that insulin resistance is primarily a risk factor for developing impaired glucose tolerance, while deficient pancreatic β-cell function is primarily a risk factor for progressing to diabetes once impaired glucose tolerance has developed (14, 32). This hypothesis, however, was based on insulin secretion as estimated by I_{120}/I_0, which may reflect primarily second-phase insulin secretion and which, in subjects with normal glucose tolerance, was not significantly correlated with first-phase insulin secretion as estimated by AIR_{gluc}. In fact, for subjects with normal glucose tolerance who had participated in the detailed physiologic studies, AIR_{gluc} was a significant predictor of developing diabetes (3), as was I_{30}/I_0 in a subset of the population study with normal glucose tolerance following an initial test with impaired glucose tolerance (33).

The Pima Indians have an extraordinarily high incidence of diabetes, and whether the present results may generalize to other populations is uncertain. However, a longitudinal study of Mexican Americans in which I_0 and $\Delta I_{30}/\Delta G_{30}$ were used showed similar effects of these indices on diabetes incidence (18). Moreover, risk factors for diabetes generally have shown similar effects across populations (2, 34, 35).

Conclusions

The present analyses of Pima Indians suggest that simple indices of insulin sensitivity and secretion may be useful surrogates for more sophisticated measures in epidemiologic studies. Any of the indices based on fasting serum insulin concentrations (I_0, ISI_0, HOMA-IR) provides a reasonable approximation of the effect of insulin sensitivity. Assessment of the effect of insulin secretion is more difficult, but the CIR appears to be the most useful index in this respect, particularly when measured in the 30-minute postload sample.

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