Progressive Loss of β-Cell Function Leads to Worsening Glucose Tolerance in First-Degree Relatives of Subjects With Type 2 Diabetes

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OBJECTIVE — The relative roles of insulin resistance and β-cell dysfunction in the pathogenesis of impaired glucose tolerance (IGT) and type 2 diabetes are debated. First-degree relatives of individuals with type 2 diabetes are at increased risk of developing hyperglycemia.

RESEARCH DESIGN AND METHODS — We evaluated the evolution of insulin sensitivity, β-cell function, glucose effectiveness, and glucose tolerance over 7 years in 33 nondiabetic, first-degree relatives of type 2 diabetic individuals using frequently sampled tolbutamide-modified intravenous and oral glucose tolerance tests.

RESULTS — Subjects gained weight, and their waist circumference increased ($P < 0.05$). Insulin sensitivity, the acute insulin response to glucose, and glucose effectiveness did not change significantly. However, when we accounted for the modulating effect of insulin sensitivity on insulin release, β-cell function determined as the disposition index decreased by 22% ($P < 0.05$). This decrease was associated with declines in intravenous and oral glucose tolerance ($P < 0.05$ and $P < 0.001$, respectively). Of the subjects with normal glucose tolerance at the first assessment, we compared those who progressed to IGT with those who did not. The disposition index was 50% lower in the progressors than in the nonprogressors at follow-up ($P < 0.05$).

CONCLUSIONS — The decline in glucose tolerance over time in first-degree relatives of type 2 diabetic individuals is strongly related to the loss of β-cell function. Thus, early interventions to slow the decline in β-cell function should be considered in high-risk individuals.

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Abbreviations: AIR_g, acute insulin response to glucose; AUC_G, area under the curve for glucose; DI, disposition index; FSIGT, frequently sampled intravenous glucose tolerance test; GENNID, Genetics of Non-Insulin Dependent Diabetes Mellitus; GEZI, glucose effectiveness at zero insulin; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

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

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Insulin resistance has been suggested to constitute one of the primary and key pathogenic factors for the development of glucose intolerance and type 2 diabetes (1,2). This concept has recently been revisited (3) because these studies did not truly examine β-cell function by accounting for the now well-recognized effect of insulin resistance to increase insulin release (4). The potential role of impaired β-cell function in the deterioration of glucose tolerance has been supported by cross-sectional studies in first-degree relatives of individuals with type 2 diabetes (5,6), in subjects with impaired glucose tolerance (IGT) (7), and in women with a history of gestational diabetes (8) or polycystic ovary syndrome (9).

Glucose effectiveness, a measure of insulin-independent glucose uptake, has also been shown to be an important determinant of glucose tolerance (10). This parameter has been demonstrated to be reduced in individuals with type 2 diabetes (11) and at baseline in offspring of couples with type 2 diabetes who subsequently developed diabetes (12) and to change with intervention (13). However, whether a progressive decrease in glucose effectiveness occurs during the progression to type 2 diabetes has, to the best of our knowledge, not been examined.

First-degree relatives of individuals with type 2 diabetes are at increased risk of developing glucose intolerance and diabetes. As longitudinal studies in these subjects should provide insight into the pathogenesis of hyperglycemia, we assessed the evolution of insulin sensitivity, β-cell function, glucose effectiveness, and glucose tolerance over a period of 7 years in a group of first-degree relatives of individuals with type 2 diabetes and measured adiponectin to examine whether this could predict a decline in glucose tolerance. Our primary hypothesis was that these subjects would be insulin resistant but that β-cell function would decline over time and be reflected by worsening glucose tolerance. Further, we hypothesized that glucose effectiveness might also

decline progressively and contribute to the decrease in glucose tolerance.

RESEARCH DESIGN AND METHODS

— The subjects were 33 (9 male and 24 female) Caucasian, nondiabetic, first-degree relatives of individuals with type 2 diabetes. Twenty-six subjects had participated in the American Diabetes Association's Genetics of Non-Insulin Dependent Diabetes Mellitus (GENNID) Study (14) and returned 7 years later for the follow-up study. These 26 subjects had both a frequently sampled intravenous glucose tolerance test (FSIGT) and an oral glucose tolerance test (OGTT). An additional 7 individuals had not participated in the GENNID Study, and their first assessment was done by FSIGT only, whereas their follow-up study 9 years later involved both an FSIGT and an OGTT. At both times they were studied, all subjects were apparently healthy and had not been counseled or studied between the two assessments. The study was reviewed and approved by the Human Subjects Review Committee at the University of Washington, and written informed consent was obtained from each participant.

Weight, height, waist, and hip circumferences and blood pressure were measured at the first assessment for the 26 GENNID Study subjects and at the second assessment for all 33 subjects. A tolbutamide-modified FSIGT was performed to quantify insulin sensitivity, insulin release, and intravenous glucose tolerance (4). Briefly, glucose (11.4 g/m^2 body surface area) was infused intravenously over 1 min, and 20 min later tolbutamide (125 mg/m^2 body surface area) was administered intravenously over 30 s. Three basal blood samples were drawn before glucose injection, and 32 samples were drawn over the 240 min after glucose administration for glucose and insulin measurements.

A 75-g OGTT was performed after a 10-h overnight fast. Samples were drawn at baseline and every 30 min after glucose ingestion up to 120 min. Subjects were classified as having normal glucose tolerance (NGT), IGT, or diabetes (15).

Assays

Plasma glucose was measured using the glucose oxidase method. Plasma insulin concentrations were measured by radioimmunoassay (4), in which the primary antibody detects insulin, proinsulin, and proinsulin conversion intermediates on an equimolar basis. Fasting plasma triglycerides and total cholesterol were determined by enzymatic analytical chemistry. HDL cholesterol was measured after heparin–manganese sulfate precipitation. LDL cholesterol was calculated using the Friedewald equation. Fasting adiponectin was measured as described previously (16).

Calculations and statistics

Insulin sensitivity was quantified as the insulin sensitivity index (S_I) using the minimal model of glucose kinetics. The minimal model also provides an estimate of glucose effectiveness at basal insulin (S_g), which can be used to calculate glucose effectiveness at zero insulin (GEZI) as S_g − (basal insulin × S_I) (13). Insulin release was quantified as the acute insulin response to glucose (AIR_g), the mean of the incremental insulin response between 2 and 10 min after glucose injection.

The disposition index (DI), which provides a measure of β-cell function, was calculated as $S_I \times AIR_g$, based on the known hyperbolic relationship between these two variables (4), a relationship that is not affected by sex or differences in glucose tolerance (4,17). Percentile rankings of DI were calculated on the basis of data from our laboratory (4). As the relationship between S_I and AIR_g is nonlinear and to allow plotting of the data from initial and follow-up assessments on the hyperbolae for the control cohort, geometric means were calculated for S_I, AIR_g, and DI.

The glucose disappearance constant (K_g) provides an estimate of intravenous glucose tolerance. It was calculated as the slope of the linear regression line relating the natural logarithm of the glucose concentration over time from 10 to 19 min after glucose administration. The trapezoidal rule was used to calculate the incremental area under the curve for glucose (AUC_G) during the OGTT as a measure of oral glucose tolerance.

Data are presented as arithmetic means ± SD unless otherwise indicated. Comparisons of data obtained at the two time points were performed by paired *t* test or by a Mann-Whitney *U* test. Relationships between continuous variables were assessed using Spearman's correlation coefficient and by multiple regression analysis. Multiple linear regression analysis was also performed to determine whether progression to IGT was related to a given variable at the second assessment while adjusting for the baseline value. A two-sided $P \leq 0.05$ was considered significant.

RESULTS

Evolution of demographic characteristics over time

At the first assessment, subjects were 37.9 ± 12.1 years of age. The time between the first and second assessments was 7.3 ± 1.2 years and during this period the 33 individuals remained apparently healthy.

As shown in Table 1, the average weight gain was 7.6 kg. Thus, although the cohort's average BMI placed them in the range of overweight at the first assessment, at follow-up their average BMI was in the obese range. Waist circumference increased, without a change in hip circumference. In parallel with this increase in central adiposity, LDL cholesterol and triglycerides increased, as did systolic blood pressure (Table 1). Fasting glucose or insulin levels did not change.

Evolution of insulin sensitivity, insulin release, β-cell function, and glucose effectiveness over time

At their first assessment, subjects had an S_I of 4.6 ± 2.7 × 10^{-5} min^{-1}/pmol), which did not change during follow-up ($P = 0.56$) (Table 1), consistent with the unchanged fasting insulin levels. Adiponectin also did not change over time ($P = 0.24$) (Table 1). In contrast, insulin release, measured as AIR_g, was 16% lower at the second assessment ($P = 0.08$). β-Cell function, determined as DI, decreased by 22% over the same period ($P = 0.02$) (Table 1). Glucose effectiveness did not change over time whether measured at basal insulin ($P = 0.22$) (Table 1) or when corrected to zero insulin ($P = 0.39$) (Table 1).

We examined the percentile ranking of DI for these high-risk subjects using equations previously published for this relationship (4). The first-degree relatives had a percentile ranking of 15 at their first assessment, and this decreased to 3 at the second assessment (Fig. 1*A*). In line with the decrease in β-cell function, intravenous glucose tolerance (K_g) decreased significantly ($P = 0.03$) (Table 1).

We examined whether the evolution of insulin sensitivity, insulin secretion, or glucose effectiveness was correlated to the change in weight or in waist circumference over time. We observed no correlation between weight gain or increased abdominal contour and insulin sensitiv-

Table 1—*Evolution over time of demographics, insulin sensitivity, β-cell function, glucose tolerance, and cardiovascular risk factors in 33 first-degree relatives (24 women and 9 men) of subjects with type 2 diabetes*

	First assessment	Second assessment	*P* value
Age (years)	37.9 ± 12.1	45.2 ± 11.8	<0.0001
Weight (kg)	84.7 ± 15.1	92.3 ± 20.2	0.0008
BMI (kg/m^2)	28.6 ± 4.4	31.4 ± 6.4	0.0003
Waist circumference (cm)	100 ± 11	105 ± 15	0.04
Hip circumference (cm)	110 ± 7	110 ± 9	0.23
Waist-to-hip ratio	0.91 ± 0.08	0.95 ± 0.09	0.0003
Fasting glucose (mmol/l)	5.14 ± 0.47	5.25 ± 0.47	0.51
Fasting insulin (pmol/l)	76.6 ± 43.5	76.4 ± 52.6	0.99
Adiponectin (μg/ml)	13.2 ± 1.1	12.1 ± 1.1	0.24
S_I ($\times 10^{-5}$ min^{-1}/pmol)	4.6 ± 2.7 (3.9)	4.3 ± 3.1 (3.0)	0.56
AIR_g (pmol/l)	403 ± 297 (318)	338 ± 239 (252)	0.08
DI ($\times 10^{-5}$ min^{-1})	1,599 ± 1,094 (1,240)	1,253 ± 816 (756)	0.02
S_g ($\times 10^{-2}$ min^{-1})	1.83 ± 0.48	1.70 ± 0.52	0.22
GEZI ($\times 10^{-2}$ min^{-1})	1.54 ± 0.51	1.45 ± 0.54	0.39
K_g (%/min)	1.70 ± 0.55	1.47 ± 0.42	0.03
2-h glucose (mmol/l)*	7.38 ± 1.72	8.38 ± 2.56	0.03
AUC_G (mmol/l × min)*	280 ± 139	392 ± 195	0.0003
Cholesterol (mg/dl)	181 ± 32	187 ± 25	0.006
HDL cholesterol (mg/dl)	45 ± 9	43 ± 10	0.36
LDL cholesterol (mg/dl)	119 ± 27	125 ± 23	0.02
Triglycerides (mg/dl)	85 ± 50	96 ± 39	0.048
Systolic blood pressure (mmHg)	115 ± 13	122 ± 14	0.005
Diastolic blood pressure (mmHg)	72 ± 11	75 ± 10	0.23

Data are arithmetic means ± SD with geometric means where appropriate in parentheses. *P* values are for comparisons between assessments. *Twenty-six subjects had an OGTT at both assessments.

ity. In contrast, the change in weight was inversely correlated with the change in DI ($r = -0.36$, $P = 0.02$), whereas the change in waist circumference was inversely correlated with the changes in AIR_g ($r = -0.50$, $P = 0.02$) and DI ($r = -0.46$, $P = 0.07$). No significant correlations were found with glucose effectiveness.

Evolution of oral glucose tolerance over time

Oral glucose tolerance, measured as AUC_G, decreased over the 7-year follow-up period ($P = 0.0003$) (Table 1). The 2-h glucose level also increased ($P = 0.03$) (Table 1), and this was associated with changes in glucose tolerance categories. Thus, among the 16 subjects who had NGT at the first assessment, 6 developed IGT 7 years later, whereas 10 retained NGT. Among the 10 subjects with IGT at the first assessment, two reverted to NGT, four still had IGT, and 4 progressed to diabetes.

Determinants of worsening glucose tolerance over time

To further assess the variables determining the progression from NGT to IGT, we examined the 16 subjects with NGT at the first assessment. The 10 subjects who maintained NGT during the follow-up period (nonprogressors) were compared with the 6 subjects who developed IGT (progressors). At the first assessment, when all subjects had NGT, progressors and nonprogressors values for S_I, AIR_g, DI, or S_g did not differ significantly, whereas GEZI was lower (Table 2). Over time, S_I declined by 12% in the progressors and by 3% in the nonprogressors, whereas AIR_g decreased by 25% in the progressors compared with 11% in the nonprogressors. Thus, β-cell function, determined as DI, decreased by 38% in the progressors and by 20% in the nonprogressors (Table 2). These differences in the responses translated to a decline in the percentile rankings for DI from 21 to 5 in the progressors and from 45 to 35 in the nonprogressors (Fig. 1*B*). At the end of follow-up, β-cell function was lower in the progressors than in the nonprogressors ($P = 0.05$). Further, progression to IGT was associated with a lower DI at follow-up after adjustment for the baseline DI (regression coefficient −0.598, $P = 0.04$). Thus, the decline in DI was greater for progressors than for nonprogressors (518 vs. 289). S_I and AIR_g, however, were not associated with progression to IGT in similar linear regression models. As regards glucose effectiveness, GEZI declined by 10% in the progressors and by 11% in the nonprogressors. Thus, although this parameter was significantly different at the first assessment, at the second assessment this measure only tended to be lower in the progressors ($P = 0.10$) (Table 2). Adiponectin levels were not different between progressors and nonprogressors at the first or second assessment (Table 2).

In keeping with the evolution of β-cell function, intravenous glucose tolerance and oral glucose tolerance did not differ between the progressors and nonprogressors at the first assessment. However, both were significantly lower in the progressors at follow-up ($P = 0.03$ and $P = 0.001$, respectively) (Table 2).

As in the subjects who initially had NGT, in the 10 subjects who initially had IGT, the percentile rankings for DI changed in line with the conversion to different glucose tolerance states. Thus, in the four subjects who progressed to diabetes, the percentile ranking decreased from 4 to 1, whereas in the six subjects who did not progress, it evolved from 6 to 9.

CONCLUSIONS

— The relative importance of insulin resistance and β-cell dysfunction in the development of type 2 diabetes has been a long-standing debate (1–3,5,6,18,19). Contributing to this debate has been the lack of recognition that, as with all endocrine systems, insulin release is regulated by a feedback loop between the insulin-sensitive tissues and the β-cell (4). Thus, when insulin sensitivity decreases, the insulin response should increase reciprocally such that β-cell function is not changed, and glucose tolerance is maintained. In the current longitudinal study, this reciprocal response did not occur, reflecting a decline in β-cell function over time. This decline was associated with a decrease in glucose tolerance in the whole cohort and the development of diabetes in 4 of the 33 subjects. Among the 16 subjects who initially had NGT, 6 developed IGT. Progression from NGT to IGT was associated with a reduction in β-cell function, which was significantly different from the response in the 10 subjects who retained NGT. Thus, a progressive loss of β-cell function characterizes the deterioration in glucose tolerance that

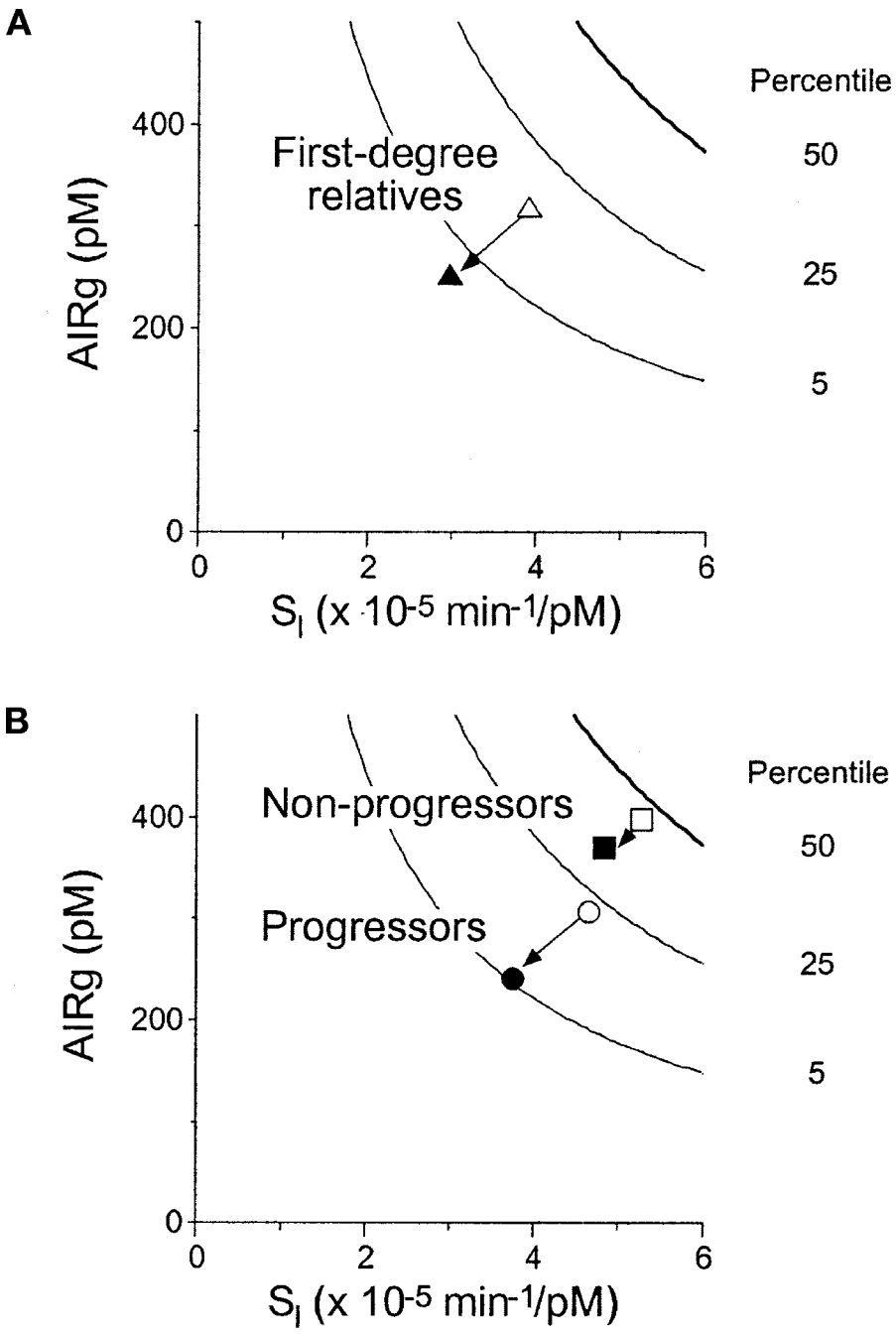

Figure 1—*S_I and the AIR_g at the first (△) and second (▲) assessments for* (A) *all 33 first-degree relatives and* (B) *6 individuals who progressed from NGT to IGT (progressors; ○ and ●) and 10 individuals who maintained NGT (nonprogressors; □ and ■). The 50th, 25th, and 5th percentiles for the relationship between S_I and AIR_g are from published equations (4). The data for each time point are presented as geometric means.*

occurs in high-risk individuals, even at an early stage of the disease process.

A number of groups are at increased risk of developing type 2 diabetes, including individuals with a family history of the disease, those with IGT, older individuals, and women with a history of gestational diabetes or polycystic ovary syndrome. Cross-sectional studies in which β-cell function was assessed by considering the insulin response relative to insulin sensitivity have demonstrated that these groups have reduced β-cell function (7,8,18,20). However, few longitudinal studies in these high-risk groups have been performed. In one study in 155 offspring of diabetic parents (2), it was concluded that insulin sensitivity was the major determinant of progression. However, this analysis did not account for the modulating effect of insulin sensitivity on the insulin response. Evidence that a decline in β-cell function is a critical determinant of deteriorating glucose tolerance comes from longitudinal studies in Pima Indians (19) and in postmenopausal women (21) and from the U.K. Prospective Diabetes Study (22). Recently, a role for impaired β-cell compensation in the progression to IGT and diabetes was also demonstrated in the Insulin Resistance Atherosclerosis Study (23) and in Hispanic women (24).

The mechanisms underlying the progressive decline in β-cell function are not fully understood. It may be related to a genetic predisposition compounded by environmental exposure such as increased caloric intake and the development of obesity. Interestingly, we found that the development of central adiposity was associated with loss of β-cell function, suggesting that changes in central or visceral fat–derived factors may predispose to β-cell dysfunction in high-risk individuals. Similarly, others have found that central body fatness and the increase in fat over time were the major predictors of a decline in the homeostasis model assessment insulin secretion index in women with a family history of diabetes (25).

The subjects in the current study were relatively insulin resistant, in keeping with studies in offspring of diabetic parents (2). Although subjects gained weight over time, their insulin sensitivity did not decline, consistent with data from the Pima Indians, in whom little change in insulin sensitivity occurred in subjects who gained weight and progressed to diabetes (19). This result may indicate that insulin resistance has been established and is near maximal so that additional weight gain does not discernibly reduce insulin sensitivity. Consistent with this finding, adiponectin did not change over time. β-Cell function was also poor at the first assessment (percentile ranking 15), and decreased to percentile ranking 3 during follow-up. Thus, insulin resistance is likely to be involved in the pathogenesis of type 2 diabetes, but the progressive loss of β-cell function appears to be the critical determinant for disease progression from NGT to IGT and then to type 2 diabetes.

Our observations were made using insulin measurements. Because insulin clearance is affected by insulin sensitivity,

Table 2—*Evolution over time of demographics, insulin sensitivity, β-cell function, and glucose tolerance in subjects with NGT who did or did not progress to IGT*

	First assessment			Second assessment		
	Nonprogressors	Progressors	*P* value	Nonprogressors	Progressors	*P* value
n (female/male)	10 (7/3)	6 (4/2)		10 (7/3)	6 (4/2)	
Age (years)	35.6 ± 7.7	39.2 ± 10.9	0.59	42.1 ± 8.2	46.5 ± 10.7	0.48
Weight (kg)	85.5 ± 11.9	86.1 ± 20.5	0.70	89.6 ± 10.0	100.8 ± 39.0	0.99
BMI (kg/m^2)	27.7 ± 3.2	29.3 ± 5.8	0.66	29.2 ± 2.9	34.2 ± 11.4	0.23
Waist circumference (cm)	97 ± 9	99 ± 16	0.74	103 ± 7	108 ± 29	0.59
Hip circumference (cm)	111 ± 8	111 ± 10	0.83	109 ± 7	115 ± 14	0.59
Waist-to-hip ratio	0.88 ± 0.07	0.89 ± 0.11	0.45	0.95 ± 0.07	0.93 ± 0.14	0.45
Fasting glucose (mmol/l)	5.17 ± 0.33	5.00 ± 0.28	0.36	4.94 ± 0.40	4.98 ± 0.48	0.87
Fasting insulin (pmol/l)	60.3 ± 19.7	60.2 ± 35.6	0.45	53.3 ± 19.2	97.8 ± 71.6	0.16
Adiponectin (μg/ml)	11.9 ± 2.0	15.4 ± 3.0	0.33	10.9 ± 1.5	11.4 ± 2.0	0.91
S_I ($\times 10^{-5}$ min^{-1}/pmol)	5.8 ± 2.9 (5.2)	5.1 ± 2.4 (4.6)	0.55	5.6 ± 3.2 (4.8)	4.5 ± 2.7 (3.7)	0.42
AIR_g (pmol/l)	509 ± 342 (399)	355 ± 231 (309)	0.59	452 ± 298 (372)	267 ± 130 (244)	0.16
DI ($\times 10^{-5}$ min^{-1})	2,437 ± 1,232 (2,075)	1,646 ± 888 (1,421)	0.19	1,949 ± 824 (1,786)	1,017 ± 511 (903)	0.05
S_g ($\times 10^{-2}$ min^{-1})	2.27 ± 0.36	1.63 ± 0.41	0.009	2.00 ± 0.57	1.53 ± 0.47	0.10
GEZI ($\times 10^{-2}$ min^{-1})	1.94 ± 0.38	1.36 ± 0.49	0.051	1.73 ± 0.61	1.23 ± 0.52	0.10
K_g (%/min)	2.08 ± 0.62	1.61 ± 0.45	0.08	1.73 ± 0.46	1.29 ± 0.28	0.03
2-h glucose (mmol/l)	6.15 ± 0.86	6.34 ± 0.61	0.87	6.12 ± 0.88	8.75 ± 1.18	0.001
AUC_G (mmol/l × min)	197 ± 69	207 ± 66	0.74	224 ± 76	496 ± 101	0.001

Data are arithmetic means ± SD with geometric means where appropriate in parentheses. *P* values are for the comparison between progressors and nonprogressors at the same assessment.

with clearance being less in insulin-resistant individuals (26), our findings could be said to be even more striking. Using C-peptide measurements, we probably would have found an even greater change over time. The difference between measurements using insulin and C-peptide also raises the interesting concept that DI is a measure of both changes in β-cell responsiveness and modulation of hepatic insulin extraction. The aim of this integrated adaptation is to reduce pancreatic workload while simultaneously trying to maintain glucose tolerance. Our findings highlight the severity of the β-cell defect, as the reduced insulin clearance is unable to adequately compensate to maintain hyperinsulinemia and thus glucose tolerance.

We also evaluated the possible role of glucose effectiveness, an important determinant of glucose metabolism (10). Although we did not observe a significant change in this variable over time, it was lower at the first assessment in the subjects who subsequently progressed. This finding is in keeping with those of Martin et al. (12) and suggests that a reduction in insulin-independent glucose uptake may also contribute to progression to diabetes. Further work in this area using larger cohorts will help define whether this is an important contributor.

The Diabetes Prevention Program (DPP) (27) and the Finnish Diabetes Prevention Study (28) both demonstrated that a lifestyle intervention decreases the risk of development of diabetes by 58%. Further, the DPP found that metformin reduced the risk of development of diabetes by 31%, whereas the STOP-NIDDM, Troglitazone in Prevention of Diabetes (TRIPOD), and Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) studies reported 25, 50, and 60% risk reductions with acarbose, troglitazone, and rosiglitazone, respectively (29–31). The improvement in glucose tolerance with intervention may be the result of improved β-cell function along with enhanced insulin sensitivity, as observed after weight loss (32) and lifestyle and metformin interventions in the DPP (33). An improvement in insulin sensitivity and preservation of β-cell function was also demonstrated in the TRIPOD study (29). Thus, we believe that individuals with a family history of type 2 diabetes should be closely followed, and serious consideration should be given to interventions with lifestyle modification or medications to try to prevent the development of hyperglycemia that is the result of both insulin resistance and, importantly, a progressive loss of β-cell function.

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References

1. Lillioja S, Mott DM, Howard BV, Bennett PH, Yki-Jarvinen H, Freymond D, Nyomba BL, Zurlo F, Swinburn B, Bogardus C: Impaired glucose tolerance as a disorder of insulin action. Longitudinal and cross-sectional studies in Pima Indians. *N Engl J Med* 318:1217–1225, 1988
2. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern*

Med 113:909–915, 1990
3. Kahn SE: The relative contributions of insulin resistance and β-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 46:3–19, 2003
4. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, et al.: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 42:1663–1672, 1993
5. Pimenta W, Korytkowski M, Mitrakou A, Jenssen T, Yki-Jarvinen H, Evron W, Dailey G, Gerich J: Pancreatic β-cell dysfunction as the primary genetic lesion in NIDDM: evidence from studies in normal glucose-tolerant individuals with a first-degree NIDDM relative. *JAMA* 273:1855–1861, 1995
6. van Haeften TW, Dubbeldam S, Zonderland ML, Erkelens DW: Insulin secretion in normal glucose-tolerant relatives of type 2 diabetic subjects: assessments using hyperglycemic glucose clamps and oral glucose tolerance tests. *Diabetes Care* 21:278–282, 1998
7. Larsson H, Ahren B: Failure to adequately adapt reduced insulin sensitivity with increased insulin secretion in women with impaired glucose tolerance. *Diabetologia* 39:1099–1107, 1996
8. Ward WK, Johnston CLW, Beard JC, Benedetti TJ, Halter JB, Porte D Jr: Insulin resistance and impaired insulin secretion in subjects with histories of gestational diabetes mellitus. *Diabetes* 34:861–869, 1985
9. Dunaif A, Finegood DT: β-Cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 81:942–947, 1996
10. Best JD, Kahn SE, Ader M, Watanabe RM, Ni TC, Bergman RN: Role of glucose effectiveness in the determination of glucose tolerance. *Diabetes Care* 19:1018–1030, 1996
11. Welch S, Gebhart SS, Bergman RN, Phillips LS: Minimal model analysis of intravenous glucose tolerance test-derived insulin sensitivity in diabetic subjects. *J Clin Endocrinol Metab* 71:1508–1518, 1990
12. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR: Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet* 340: 925–929, 1992
13. Kahn SE, Klaff LJ, Schwartz MW, Beard JC, Bergman RN, Taborsky GJ Jr, Porte D Jr: Treatment with a somatostatin analog decreases pancreatic β-cell and whole body sensitivity to glucose. *J Clin Endocrinol Metab* 71:994–1002, 1990
14. Raffel LJ, Robbins DC, Norris JM, Boerwinkle E, DeFronzo RA, Elbein SC, Fujimoto W, Hanis CL, Kahn SE, Permutt MA, Chiu KC, Cruz J, Ehrmann DA, Robertson RP, Rotter JI, Buse J: The GENNID Study: a resource for mapping the genes that cause NIDDM. *Diabetes Care* 19: 864–872, 1996
15. American Diabetes Association: Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 20:1183–1197, 1997
16. Tonelli J, Li W, Kishore P, Pajvani UB, Kwon E, Weaver C, Scherer PE, Hawkins M: Mechanisms of early insulin-sensitizing effects of thiazolidinediones in type 2 diabetes. *Diabetes* 53:1621–1629, 2004
17. Utzschneider KM, Prigeon RL, Carr DB, Hull RL, Tong J, Shofer JB, Retzlaff BM, Knopp RH, Kahn SE: Impact of differences in fasting glucose and glucose tolerance on the hyperbolic relationship between insulin sensitivity and insulin responses. *Diabetes Care* 29:356–362, 2006
18. Jensen CC, Cnop M, Hull RL, Fujimoto WY, Kahn SE: β-Cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the U.S. *Diabetes* 51:2170–2178, 2002
19. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787–794, 1999
20. Ehrmann DA, Sturis J, Byrne MM, Karrison T, Rosenfield RL, Polonsky KS: Insulin secretory defects in polycystic ovary syndrome: relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. *J Clin Invest* 96:520–527, 1995
21. Larsson H, Ahren B: Glucose intolerance is predicted by low insulin secretion and high glucagon secretion: outcome of a prospective study in postmenopausal Caucasian women. *Diabetologia* 43:194–202, 2000
22. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC: UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years: UK Prospective Diabetes Study (UKPDS) Group. *Diabet Med* 15:297–303, 1998
23. Festa A, Williams K, D'Agostino R Jr, Wagenknecht LE, Haffner SM: The natural course of β-cell function in nondiabetic and diabetic individuals: the Insulin Resistance Atherosclerosis Study. *Diabetes* 55:1114–1120, 2006
24. Xiang AH, Wang C, Peters RK, Trigo E, Kjos SL, Buchanan TA: Coordinate changes in plasma glucose and pancreatic β-cell function in Latino women at high risk for type 2 diabetes. *Diabetes* 55: 1074–1079, 2006
25. Kriketos AD, Carey DG, Jenkins AB, Chisholm DJ, Furler SM, Campbell LV: Central fat predicts deterioration of insulin secretion index and fasting glycaemia: 6-year follow-up of subjects at varying risk of type 2 diabetes mellitus. *Diabet Med* 20:294–300, 2003
26. Bonora E, Zavaroni I, Coscelli C, Butturini U: Decreased hepatic insulin extraction in subjects with mild glucose intolerance. *Metabolism* 32:438–446, 1983
27. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
28. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
29. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51: 2796–2803, 2002
30. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 359:2072–2077, 2002
31. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368:1096–1105, 2006
32. Utzschneider KM, Carr DB, Barsness SM, Kahn SE, Schwartz RS: Diet-induced weight loss is associated with an improvement in β-cell function in older men. *J Clin Endocrinol Metab* 89:2704–2710, 2004
33. Kitabchi AE, Temprosa M, Knowler WC, Kahn SE, Fowler SE, Haffner SM, Andres R, Saudek C, Edelstein SL, Arakaki R, Murphy MB, Shamoon H: Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: effects of lifestyle intervention and metformin. *Diabetes* 54:2404–2414, 2005