Original Article

Coordinate Changes in Plasma Glucose and Pancreatic β-Cell Function in Latino Women at High Risk for Type 2 Diabetes

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The purpose of this study was to examine longitudinally the relationship among glucose levels, pancreatic β-cell function, and insulin resistance in women at high risk for type 2 diabetes. Oral glucose tolerance tests (OGTTs) and intravenous glucose tolerance tests (IVGTTs) were performed at 15-month intervals for up to 5 years or until fasting plasma glucose exceeded 140 mg/dl in Hispanic women with recent gestational diabetes. Data were analyzed *1*) to compare changes in insulin sensitivity, β-cell function, and glucose levels between women who had diabetes at one or more visits and women who remained diabetes free and *2*) to determine longitudinal patterns of change in glucose levels and acute β-cell compensation for insulin resistance. Seventy-one women provided data from a total of 280 paired OGTTs and IVGTTs during a median follow-up of 46 months. Compared with the 47 women who remained free of diabetes, the 24 who either had diabetes ($n = 9$) or developed it during follow-up ($n = 15$) had higher baseline glucose levels and lower acute β-cell compensation for insulin resistance. Baseline insulin sensitivity was low in both groups and did not change significantly during follow-up. Fasting and 2-h glucose levels increased more rapidly in the diabetic group despite a decline in acute β-cell compensation that was significantly slower than the decline in women who did not develop diabetes. This paradox was explained by an accelerated rise in glucose levels for any decline in β-cell compensation when β-cell compensation reached ~10% of normal, a level that was reached in the women who had or developed diabetes but not in the women who remained diabetes free. These findings define a pathogenesis for type 2 diabetes in one high-risk group that is characterized by a relatively long-term decline in acute β-cell compensation for chronic insulin resistance that is attended by slowly rising glucose levels. Only relatively late in this process do glucose levels rise rapidly and into the diabetic range.
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AIRg, acute insulin response to intravenous glucose; GDM, gestational diabetes mellitus; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test.

Type 2 diabetes is defined by glucose levels in the diabetic range that are caused by inadequate pancreatic β-cell compensation for insulin resistance (1). Longitudinal studies indicate that insulin resistance precedes the development of diabetes by many years and may worsen during progression to diabetes (2–5). Inadequate insulin secretion is a less consistent finding long before diabetes develops, but declining function clearly occurs during the progression from normal glucose tolerance to diabetes (4) and during worsening of existing diabetes (6). At the present time, relatively little is known about the relationship among changes in insulin sensitivity (S_I), insulin secretion, and glucose levels during the development of type 2 diabetes. We have been performing serial measurements of S_I, insulin secretion, and glucose tolerance in a cohort of Hispanic women at high risk for type 2 diabetes by virtue of a recent history of gestational diabetes mellitus (GDM). In the present report, we examine the relationship between β-cell function and glucose levels in those women.

RESEARCH DESIGN AND METHODS

Subjects for the present report were part of a cohort of 150 islet cell antibody–negative women who agreed to participate in a longitudinal study of the pathogenesis of type 2 diabetes after GDM. Selection of the original cohort has been described in detail (7,8). Briefly, all Latino women referred to Los Angeles County Women's Hospital for management of GDM between August 1993 and March 1995 were asked to participate if they met all of the following criteria: *1*) gestational age between 28 and 34 weeks, *2*) no current or prior insulin therapy, *3*) all fasting serum glucose concentrations <130 mg/dl (7.2 mmol/l) during pregnancy, *4*) otherwise uncomplicated singleton pregnancy, and *5*) both parents and at least three of four grandparents from Mexico, Guatemala, or El Salvador. All women had detailed metabolic testing during the 3rd trimester, as described previously (7,8). They were asked to return for a 75-g oral glucose tolerance test (OGTT) 6 months postpartum and then for an OGTT and an intravenous glucose tolerance test (IVGTT) at 15 months postpartum and every 15 months thereafter. Information on contraceptive use and pregnancies was collected at each visit. At the time of diagnosis of impaired glucose tolerance or diabetes, subjects met once with a dietitian and received advice on nutrition and daily walking. Subjects remained in follow-up until they withdrew consent, were lost to follow-up, or developed a fasting plasma glucose concentration >140 mg/dl, at which time they were referred for pharmacological treatment of their diabetes. Women who were pregnant at the time of a scheduled battery of tests were studied at least 4 months after pregnancy and at least 1 month after completion of breast-feeding. A set of tests consisting of an OGTT and IVGTT was considered to fall within a given test window if testing was completed at least 3 months before the following test window. Otherwise, the visit was recorded as missed.

For the present report, which is focused on nonpregnant women from 15 months postpartum onward, we analyzed data from all subjects who *1*) had a complete baseline set of OGTT and IVGTT in the 15- or 30-month postpartum

TABLE 1
Baseline characteristics and rates of change in women who had or developed diabetes and women who remained nondiabetic

Variable	Diabetes		*P* value†
	Yes (n = 24)*	No (n = 47)*	
Baseline			
Age (years)	33 (6)	32 (5)	0.81
BMI (kg/m^2)	32.0 (5.6)	30.4 (4.9)	0.23
Fasting glucose (mg/dl)‡	105 (16)	97 (8)	0.02
2-h glucose (mg/dl)‡	185 (55)	139 (29)	0.0008
Fasting insulin (μU/ml)‡	24.1 (12.2)	18.8 (9.3)	0.15
S_I§	1.01 (0.74)	1.68 (1.09)	0.001
AIRg¶	297 (393)	714 (714)	<0.0001
Disposition index (S_I × AIRg)‖	288 (289)	968 (577)	<0.0001
Change during follow-up ([final − initial]/time)			
Duration of follow-up (months)	44 (18)	47 (14)	0.41
BMI (kg/m^2 per year)	−0.06 (1.70)	0.50 (1.05)††	0.15
Fasting glucose (mg/dl per year)‡	19 (34)††	1 (3)**	0.01
2-h glucose (mg/dl per year)‡	28 (49)††	4 (12)**	0.02
S_I (per year)§	−0.04 (0.29)	0.04 (0.42)	0.42
AIRg (μU · ml^{-1} · min^{-1} per year)¶	−26 (99)	−96 (180)‡‡	0.04
Disposition index (per year)‖	−33 (58)**	−94 (135)‡‡	0.01

Data are means ± SD. *At any visit for "yes" and at all visits for "no." †For comparison between groups by two-group t test. ‡During 75-g OGTTs. §Calculated by minimal model analysis of IVGTT insulin and glucose data. ¶Incremental insulin area during first 10 min of IVGTT. ‖A measure of β-cell compensation for insulin resistance. **$P < 0.05$, ††$P < 0.01$, and ‡‡$P < 0.001$ significant change from baseline to final visit within each group, by paired t test.

testing window and *2*) returned for at least one additional set of OGTT and IVGTT by the 75-month postpartum test window. All subjects gave written, informed consent for participation in the study, which was approved by the institutional review board of the University of Southern California and the Los Angeles County and University of Southern California Medical Center.

Testing protocols. For baseline tests at the 15- or 30-month postpartum visit, subjects came to the General Clinical Research Center on 2 separate days, at least 48 h apart, after 8- to 12-h overnight fasts and at least 3 days on an unrestricted diet.

On one day, an OGTT was started between 0700 and 1000. Patients drank 75 g dextrose. Blood was obtained from an antecubital venous catheter before and 15, 30, 60, 90, 120, and 180 min after the glucose ingestion and placed on ice, and plasma was separated within 20 min and stored at −80°C.

On a separate day, an IVGTT was performed starting between 0700 and 1000. Dextrose (300 mg/kg) was injected over 1 min, followed in 20 min by a 5-min infusion of crystalline human insulin (0.03 unit/kg). Arterialized venous blood was drawn into iced tubes before (n = 2) and for 240 min after (n = 32) the dextrose injection. Plasma was separated within 20 min and stored at −80°C.

During follow-up, OGTTs and IVGTTs were performed as they were at baseline.

Laboratory analysis. Glucose was measured by glucose oxidase (Glucose Analyzer II; Beckman, Brea, CA). Insulin was measured by a radioimmunoassay (Novo Pharmaceuticals, Danbury, CT) that measured insulin and proinsulin. Anti-human islet cell antibodies in plasma were measured in the laboratory of Dr. Jerry Palmer using indirect immunofluorescence with an assay detection limit of 1 Juvenile Diabetes Foundation unit. Inclusion in the study cohort required a value below the detection limit.

Data analysis. Diabetes was diagnosed by OGTTs using the criteria of the American Diabetes Association (1). IVGTT results were analyzed using the MINMOD program (9) to obtain measures of fractional glucose disappearance due to an increase in insulin above the basal level (S_I). The acute insulin response to intravenous glucose (AIRg) was calculated by the trapezoid rule as the incremental area under the insulin curve during the first 10 min after the glucose injection. The product of S_I and AIRg (the disposition index) was calculated as a measure of acute pancreatic β-cell compensation for insulin resistance (10–12).

Baseline characteristics were compared by two-group t tests between women who had diabetes at one or more visits and women who remained diabetes free at all visits. OGTT insulin values, S_I, and AIRg were log-transformed, and disposition index was squared-root transformed before the t tests to meet the normal distributional assumption. To take into account different follow-up times among members of the cohort, changes during follow-up were expressed as rates ([last observation − baseline observation]/[follow-up time]). Rates of change were compared between diabetic and nondiabetic groups by two-group t tests. Wilcoxon's rank-sum tests were also performed, and results were consistent with the two-group t tests; only results of the t tests are reported.

To determine whether glucose changed equally for a given change in β-cell function across the range of function observed in the cohort, 15-month follow-up intervals were ordered according to disposition index at their start and then grouped by quartiles of a continuous distribution of starting disposition index. Generalized linear models with identity link function were used to regress change in glucose on change in disposition index for each quartile of starting disposition index. The general estimating equation approach was used to adjust for the correlation of multiple intervals in each woman and to estimate and compare the rates of change in glucose per change in disposition index among quartiles of starting disposition index. All data from all women with paired measurements at the beginning and end of a 15-month observation period were used for this analysis.

Data are presented in tables and text in their original scales as means ± SD. All statistical tests were two sided with significance level defined as <0.05.

RESULTS

Baseline characteristics. Seventy-one women met the inclusion criteria for this report. At baseline testing, 29 women had normal glucose tolerance, 33 had impaired tolerance, and 9 had diabetes with fasting plasma glucose <140 mg/dl. Five of the 29 women with normal glucose tolerance at baseline and 10 of the 33 women with impaired glucose tolerance at baseline developed diabetes by the end of the observation period. The 24 women who either had diabetes at baseline or developed it during follow-up had higher baseline glucose levels, greater insulin resistance, and worse β-cell function than the 47 women who remained nondiabetic at all visits (Table 1). The two groups were similar in baseline age, BMI, and fasting insulin levels.

Changes during follow-up. The median duration of follow-up was 46 months after the baseline visit. Twenty-eight women had all five possible visits from 15 to 75 months postpartum, 20 had four visits, 13 had three visits, and 10 had two visits.

Durations of follow-up were similar for diabetic and nondiabetic groups (Table 1). Progestin-only contraception, which we observed to be associated with a risk of diabetes during breast-feeding in a separate study (13),

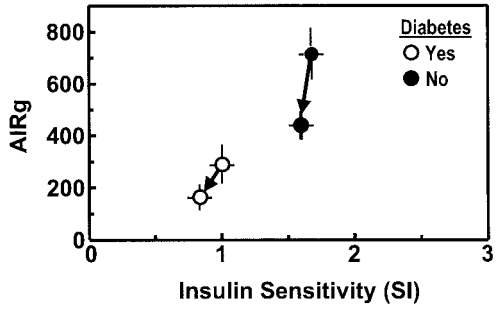

FIG. 1. Coordinate changes in S_I and AIRg. Open circles represent women who had diabetes at baseline or developed it during follow-up. Closed symbols represent women who remained free of diabetes at all visits. Arrows denote directions of change between first and last visits (mean follow-up of 44 ± 18 and 47 ± 14 months, respectively).

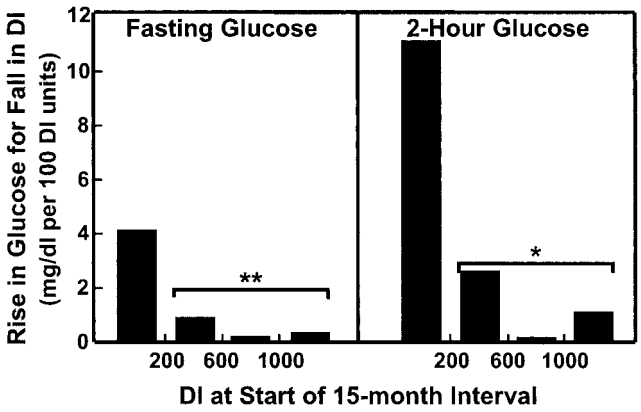

FIG. 3. Rise in OGTT fasting (*left*) or 2-h (*right*) glucose per 100-unit fall in disposition index for all 15-month follow-up intervals (n = 197), grouped according to quartile of disposition index at the beginning of the follow-up interval. **P = 0.002, *P = 0.03 vs. quartile with starting disposition index <200. There were no significant differences for change in fasting or 2-h glucose per change in disposition index among other quartiles of starting disposition index (P > 0.38).

was used by 29% of women who developed diabetes and 19% of women who did not (P = 0.34). Pregnancies, which we found to be associated with an increased risk of diabetes in a prior study (14), occurred in 42% of women who developed diabetes and 36% who did not (P = 0.65). The diabetic group tended to have stable weight, perhaps in part because of dietary advice that was provided at the diagnosis of impaired glucose tolerance or diabetes. The group that remained diabetes free gained significant weight during follow-up. S_I, which was low at baseline in both groups, did not change significantly in either group (Table 1 and Fig. 1). The diabetic group had a more rapid rise in glucose levels and a slower decline in the AIRg (Table 1 and Fig. 1) and β-cell compensation for insulin resistance, expressed as the disposition index, than women who remained free of diabetes. To determine whether the slower decline in disposition index in the group with diabetes might be due to the fact that the disposition index reached zero in some individuals, we repeated the analysis after excluding 11 intervals that contained a disposition index of zero. Nine of the excluded intervals were from seven women in the diabetic group, and two of the intervals were from two women in the nondiabetic group. The rate of rise in fasting glucose (9 ± 12 vs. 1 ± 3 mg/dl per year; P = 0.01) and 2-h glucose (15 ± 17 vs. 4 ± 12 mg/dl per year; P = 0.02) remained greater in the women who had or developed diabetes, despite a rate of fall in the disposition index that was lower than in women who remained diabetes free (−29 ± 58 vs. −94 ± 139, P = 0.01).

Relationship of glucose levels and their main determinants. There was discordance (Table 1) between the rate of rise in glucose levels, which was clearly greater in the women who had or developed diabetes, and the rate of fall of β-cell compensation for insulin resistance, which was greater in women who remained free of diabetes. Possible explanations for this discordance were examined by two analyses. First, to get a qualitative assessment of how glucose changed as β-cell function fell, we plotted relationships between the disposition index and both fasting and 2-h glucose levels from OGTTs for women who had or developed diabetes and for women who remained free of diabetes (Fig. 2). Data were ordered relative to the final visit to minimize bias created by the fact that women who developed a fasting glucose >140 mg/dl ended follow-up at that time, generally before the 75-month visit. Levels of fasting and OGTT 2-h glucose tended to rise very slowly as the disposition index fell across a relatively wide range (i.e., from ~1,000 to ~200–400) and then rose more dramatically when the disposition index fell below values of 200–400, which it did for the group who had or developed diabetes but not for the women who remained free of diabetes.

The second analysis (Fig. 3), which was more quantita-

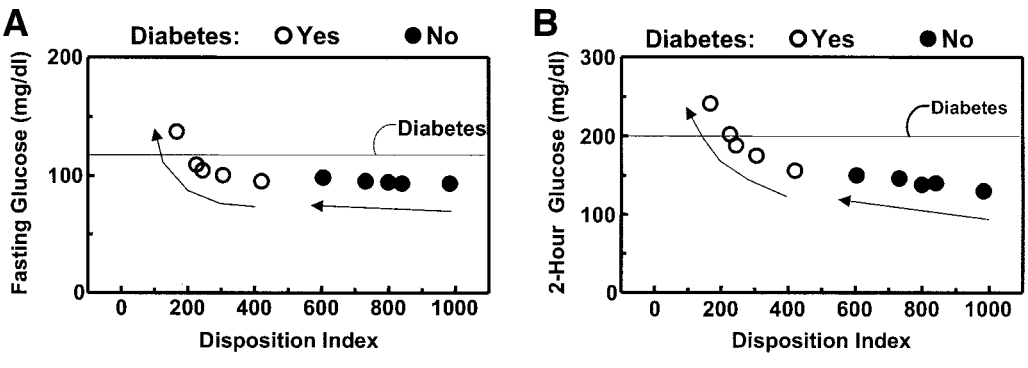

FIG. 2. Relationships between pancreatic β-cell compensation for insulin resistance (disposition index = S_I × AIRg, as described in Table 1) and fasting (*A*) or 2-h (*B*) glucose levels from OGTTs. Open circles represent mean data at 15-month intervals for women who had diabetes at baseline or developed it during follow-up. Closed symbols represent analogous data from women who remained free of diabetes at all visits. Horizontal lines denote glucose thresholds for diagnosis of diabetes, as defined in RESEARCH DESIGN AND METHODS. Arrows display direction of change during follow-up. Data in each group are plotted relative to final visits, so that symbol on the far left for each group is the average of final visits and other symbols are successive 15-month intervals before final visits.

tive, compared the change in glucose per change in disposition index during 15-month intervals with different starting values for the disposition index. This approach arranges follow-up intervals according to biology (β-cell function at the start of an interval) rather than chronology (time since pregnancy), allowing comparisons among observation intervals with different degrees of initial β-cell dysfunction. For both fasting and 2-h glucose, the increase in glucose per fall in disposition index was greatest when the starting disposition was in the lowest quartile (i.e., <200). Among the other three quartiles, there were no significant differences in rates of change in glucose per change in disposition index. This pattern persisted when the general estimating equation analysis was repeated without 11 observation intervals in which the disposition index fell to 0 (10 due to undetectable S_I; 1 due to undetectable AIRg). In this case, the rate of rise in fasting glucose per 100-unit fall in the disposition index was highest in the quartile with the lowest starting disposition index (3.1 mg/dl per 100-unit change in disposition index vs. 0.1–0.6 mg/dl per 100-unit change in the other three quartiles; $P = 0.007$). The same was true for the change in 2-h glucose (9.4 mg/dl per 100-unit change in disposition index in the lowest quartile vs. 0.1–2.3 mg/dl per 100-unit change in disposition index in the other three quartiles; $P = 0.05$).

DISCUSSION

This study provides what we believe to be novel information about how glucose levels change in relation to changing pancreatic β-cell function in one group at high-risk for type 2 diabetes, Hispanic women with a history of gestational diabetes. As a group, these women were very insulin resistant when initially studied after the index pregnancy in which GDM was diagnosed. During follow-up for up to 5 years, their insulin resistance did not change sufficiently to be detected by minimal model analysis. By contrast, AIRg, expressed relative to ambient insulin resistance as the disposition index, fell during follow-up. The insulin assay that was used measured both insulin and proinsulin, which has been reported to increase as individuals become hyperglycemic. This fact may have contributed to the observation that the fall in disposition index occurred at a slightly lower rate in the most hyperglycemic women, those who had diabetes at baseline or developed it during follow-up. Glucose levels increased more in those women, whether expressed as change per unit time or as change per unit decline in β-cell function, than was true for women who remained free of diabetes. These findings suggest that type 2 diabetes develops when declining acute β-cell compensation for insulin resistance reaches a critically low level below which additional loss of function leads to a rapid rise in glucose. Other parameters of islet cell function that were not measured by our testing procedures could decline at this stage as well.

One implication of our findings is relevant to the concept of glucose toxicity as an important determinant of falling β-cell function during the development of type 2 diabetes (15,16). To the extent that worsening hyperglycemia causes and accelerates falling β-cell function, one would expect increasing rates of decline in function as glucose levels rise. In fact, we observed the opposite pattern. Women with the greatest degree of hyperglycemia (i.e., those who had or developed diabetes during our observations) had a somewhat slower rate of decline in β-cell function compared with women who were less hyperglycemic (i.e., those who remained free of diabetes). This finding is consistent with our prior observation that changes in glucose levels during the first 3 months of troglitazone administration to a separate group of high-risk women were unrelated to the subsequent development of diabetes (17). Taken together, these observations do not support a major role for glucose toxicity in the early pathogenesis of declining β-cell function that leads to type 2 diabetes.

Another implication of our findings is relevant to clinical markers of declining β-cell function. As can be seen in Fig. 2, fasting glucose exhibited almost no systematic change across a very wide range of falling β-cell function. Thus, fasting glucose does not provide a strong clinical signal for declining function until relatively late in the progression toward diabetes. Two-hour glucose values increased more for any fall in β-cell function and could provide a stronger clinical signal of falling function. However, even changes in 2-h glucose were relatively small until β-cell function became very low and glucose levels began to rise into the diabetic range. Given the relatively poor reproducibility of 2-h glucose values during OGTTs, it seems unlikely that they will be useful in identifying declining β-cell function in individual patients in a clinical setting. More reproducible measures of average glycemia such as glycated hemoglobin, which was not measured in our cohort, warrant testing to determine whether they can provide a clinically useful approach to the tracking of β-cell decompensation during the evolution of type 2 diabetes.

Our longitudinal data provide novel information that is relevant to cross-sectional studies from many groups demonstrating poor β-cell compensation for insulin resistance in people with impaired glucose tolerance (18–25), as well as fewer longitudinal studies demonstrating that β-cell function declines during progression from normal or impaired glucose tolerance to type 2 diabetes (4,26). Our longitudinal design with frequent assessments of glucose levels, insulin resistance, and β-cell compensation provides a clearer picture of how glucose changes in relation to changing acute β-cell compensation. Our results also shed important light on the results of studies that have identified elevated glucose levels and poor β-cell function as predictors of progression from normal or impaired glucose tolerance to diabetes (5,27–29). Fig. 2 provides one explanation for these findings. Among individuals who are progressing toward diabetes, those who get there first during a fixed window of observation are the ones who were closest to diabetes when the observation commenced. They start with higher glucose levels and worse β-cell function and get to diabetes relatively quickly not because they are deteriorating more rapidly but because they are worse off to start with. Why they have progressed farther at baseline compared with other people of similar age is unclear but could be related in our subjects to their greater insulin resistance. What is clear is that predictors of diabetes in this setting are late rather than early defects in the progression to diabetes.

We included both nondiabetic and mildly diabetic women at baseline in this study. The inclusion was based on the fact that the criteria for the diagnosis of diabetes represent a division across a continuum of glucose levels in most populations. Inclusion of women who had crossed that division allowed us to examine a wider range of glycemia than would have been possible if we had limited analysis to women who started without diabetes. As a

result, we were able to identify the more rapid increase in glucose that occurs for any fall in acute β-cell function as women actually develop diabetes. Our findings provide a potential explanation for the observation of Ferrannini et al. (30) in a different Hispanic-American population that plasma glucose levels rise more rapidly during conversion from impaired or normal glucose tolerance to diabetes than from normal to impaired glucose tolerance.

The women who did and the women who did not develop diabetes were different individuals. Thus, it is not clear whether the pattern depicted in Fig. 2 represents two different biological processes or simply the same biological process viewed at different stages in its progression. Only continued follow-up of women who are not yet diabetic can resolve that distinction. However, the analysis that used all follow-up intervals and compared glucose changes per fall in disposition index provided information across a continuous spectrum of β-cell function in the cohort. That analysis revealed a clear acceleration of rising glucose for a reduction in β-cell compensation in the lowest quartile of compensation. Interestingly, the disposition index in that lowest quartile was <200, a value that represents ~10% of the mean disposition index of 1970 that we observed in 25 overweight Hispanic women who maintained normal glucose tolerance in pregnancy (8). This finding is very much like reports from animal studies of β-cell removal or destruction in which glucose changes are very small until 80–90% of cells are removed or destroyed (31). Thereafter, marked hyperglycemia occurs, much like the pattern we observed in our patients as they lost acute β-cell compensation for insulin resistance through mechanisms that remain to be identified.

In summary, we found that Hispanic women with a recent history of GDM had marked insulin resistance that changed very little, at least as assessed by the IVGTT–minimal model approach, during ~5 years of follow-up. In contrast, β-cell function, assessed as the AIRg in relation to ambient insulin resistance, declined significantly. The rate of decline was slightly less in the most hyperglycemic women, who either had or developed diabetes, than in women who remained diabetes free. Nonetheless, glucose levels rose more rapidly in the women who developed diabetes, reflecting a rapid rise in glucose for any fall in β-cell compensation when compensation was very low (<~10% of normal). These findings define at the physiological level in one high-risk group a pathogenesis for type 2 diabetes that is characterized by a long-term and relatively slow decline in insulin secretion and rise in glucose levels that occur on a background of chronic insulin resistance. Rapidly rising glucose levels occur relatively late in the process, when acute β-cell compensation falls below ~10% of normal. Clinical markers of the declining β-cell function are needed to identify patients who are progressing toward diabetes so they can be targeted for interventions to delay or prevent the disease.

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REFERENCES

1. American Diabetes Association: Diagnosis and classification of diabetes mellitus (Position Statement). *Diabetes Care* 27 (Suppl. 1): S5–S10, 2004
2. 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
3. Goldfine AB, Bouche C, Parker RA, Kim C, Kerivan A, Soeldner JS, Martin BC, Warram JH, Kahn CR: Insulin resistance is poor predictor of type 2 diabetes in individuals with no family history of disease. *Proc Natl Acad Sci U S A* 100:2724–2729, 2003
4. 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
5. Haffner SM, Miettinen H, Gaskill SP, Stern MP: Decreased insulin secretion and increased insulin resistance are independently related to the 7-year risk of NIDDM in Mexican Americans. *Diabetes* 44:1386–1391, 1995
6. UKPDS Study Group: Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995
7. Buchanan TA, Xiang A, Kjos SL, Lee WP, Trigo E, Nader I, Bergner A, Palmer JL, Peters RK: Gestational diabetes mellitus: antepartum metabolic characteristics that predict postpartum glucose intolerance and type 2 diabetes. *Diabetes* 47:1302–1310, 1998
8. Xiang AH, Peters RK, Trigo E, Kjos SL, Lee WP, Buchanan TA: Multiple metabolic defects during late pregnancy in women at high risk for type 2 diabetes mellitus. *Diabetes* 48:848–854, 1999
9. Pacini G, Bergman RN: MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. *Comput Methods Programs Biomed* 23:113–122, 1986
10. Bergman RN: Toward physiological understanding of glucose tolerance: minimal model approach. *Diabetes* 38:1512–1527, 1989
11. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte D Jr: Quantification of the relationship between insulin sensitivity and B-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 42:1663–1672, 1993
12. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Berkowitz K, Marroquin A, Goico J, Ochoa C, Azen SP: Response of pancreatic B-cells to improved insulin sensitivity in women at high risk for type 2 diabetes. *Diabetes* 49:782–788, 2000
13. Kjos SL, Peters RK, Xiang A, Thomas D, Schaefer U, Buchanan TA: Oral contraception and the risk of type 2 diabetes in Latino women with prior gestational diabetes. *JAMA* 280:533–538, 1998
14. Peters RK, Kjos SL, Xiang A, Buchanan TA: Long-term diabetogenic effect of a single pregnancy in women with prior gestational diabetes mellitus. *Lancet* 347:227–230, 1996
15. Leahy JL, Bonner-Weir S, Weir GC: β-Cell dysfunction induced by chronic hyperglycemia: current ideas on mechanism of impaired glucose-induced insulin secretion. *Diabetes Care* 15:442–455, 1992
16. Weir GC, Bonner-Weir S: Five stages of evolving β-cell dysfunction during progression to diabetes. *Diabetes* 53 (Suppl. 3): S16–S21, 2004
17. 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 B-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51:2769–2803, 2002
18. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA: Beta-cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. *J Clin Endocrinol Metab* 90:493–500, 2005
19. Ehrmann DA, Breda E, Cavaghan MK, Bajramovic S, Imperial J, Toffolo G, Cobelli C, Polonsky KS: Insulin secretory responses to rising and falling glucose concentrations are delayed in subjects with impaired glucose tolerance. *Diabetologia* 45:509–517, 2002
20. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Pettiti M, Natali A, Mari A, DeFronzo RA: Predominant role of reduced beta-cell sensitivity to glucose over insulin resistance in impaired glucose tolerance. *Diabetologia* 46:1211–1219, 2005
21. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA: Beta cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia* 47:31–39, 2004

22. Sumner AE, Farmer NM, Cochran CS, Sebring NG, Vanevski K, Reynolds JC, Premkumar A, Boston RC: Obese premenopausal African-American women with normal and impaired glucose tolerance have a similar degree of insulin resistance but differ in β-cell function. *Diabetes Care* 24:1978–1983, 2002
23. Weyer C, Bogardus C, Pratley RE: Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes* 48:2197–2203, 1999
24. Larsson H, Ahren B: Islet dysfunction in insulin resistance involves impaired insulin secretion and increased glucagon secretion in postmenopausal women with impaired glucose tolerance. *Diabetes Care* 23:650–657, 2000
25. Cavaghan MK, Ehrmann DA, Polonsky KS: Interactions between insulin resistance and insulin secretion in the development of glucose intolerance. *J Clin Invest* 106:329–333, 2000
26. Weyer C, Tataranni PA, Bogardus C, Pratley R: Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care* 24:89–94, 2001
27. 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
28. Osei K, Rhinesmith S, Gaillard T, Schuster D: Impaired insulin sensitivity, insulin secretion, and glucose effectiveness predict future development of impaired glucose tolerance and type 2 diabetes in pre-diabetic African Americans: implications for primary diabetes prevention. *Diabetes Care* 27:1439–1446, 2004
29. Pratley RE, Weyer C: The role of impaired early insulin secretion in the pathogenesis of type II diabetes mellitus. *Diabetologia* 44:929–945, 2001
30. Ferrannini E, Nannipieri M, Williams K, Gonzales C, Haffner SM, Stern MP: Mode of onset of type 2 diabetes from normal or impaired glucose tolerance. *Diabetes* 53:160–165, 2004
31. Kjems LL, Kirby BM, Welsh EM, Veldhuis JD, Straume M, McIntyre SS, Yang D, Lefebvre P, Butler PC: Decrease in β-cell mass leads to impaired pulsatile insulin secretion, reduced postprandial hepatic insulin clearance, and relative hyperglucagonemia in the minipig. *Diabetes* 50:2001–2012, 2001