Perspectives in Diabetes

Glucose Allostasis

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In many organisms, normoglycemia is achieved by a tight coupling of nutrient-stimulated insulin secretion in the pancreatic β-cell (acute insulin response [AIR]) and the metabolic action of insulin to stimulate glucose disposal (insulin action [*M*]). It is widely accepted that in healthy individuals with normal glucose tolerance, normoglycemia can always be maintained by compensatorily increasing AIR in response to decreasing *M* (and vice versa). This has been mathematically described by the hyperbolic relationship between AIR and *M* and referred to as glucose homeostasis, with glucose concentration assumed to remain constant along the hyperbola. Conceivably, glucose is one of the signals stimulating AIR in response to decreasing *M*. Hypothetically, as with any normally functioning feed-forward system, AIR should not fully compensate for worsening *M*, since this would remove the stimulus for the compensation. We provide evidence from cross-sectional, longitudinal, and prospective data from Pima Indians (n = 413) and Caucasians (n = 60) that fasting and postprandial glucose concentrations increase with decreasing *M* despite normal compensation of AIR. For this physiologic adaptation to chronic stress (insulin resistance), we propose to use the term "glucose allostasis." Allostasis (stability through change) ensures the continued homeostatic response (stability through staying the same) to acute stress at some cumulative costs to the system. With increasing severity and over time, the allostatic load (increase in glycemia) may have pathological consequences, such as the development of type 2 diabetes. *Diabetes* 52:903–909, 2003

Insulin action and secretion are the principal determinants of glycemia. In people with normal glucose tolerance (NGT), a decrease in insulin action (*M*) is accompanied by upregulation of insulin secretion (and vice versa). This is interpreted as compensation of insulin secretion for insulin resistance to maintain normoglycemia (1,2). Insulin resistance is a common consequence of obesity, for example, and represents a key factor in the pathogenesis of type 2 diabetes (3). Mathematically, the relationship between insulin secretion and insulin sensitivity is thought to be best expressed two-dimensionally by a hyperbola with the product of the two variables equalling a constant (4), named the "disposition index" (DI). The DI is considered to measure the ability of the β-cells to compensate for insulin resistance. It decreases when glucose tolerance becomes impaired (5).

While the insulin secretion/*M* hyperbola elegantly conceptualizes many cross-sectional and longitudinal observations (reviewed in 5), the physiologic signal that stimulates the compensatory increase in β-cell function in response to decreasing *M* remains unexplained. Insulin secretion is primarily substrate controlled, and glucose, the preeminent secretagogue among nutrient molecules, would be a good candidate for such a signal. Glucose-stimulated insulin secretion is primarily controlled by the enzyme glucokinase, which governs the generation of energy from glucose and acts as the β-cell glucose sensor (6).

If glucose were indeed one of the signals linking insulin resistance and β-cell compensation, insulin secretion should not fully compensate for worsening insulin resistance, since this would remove the stimulus for the compensation. We therefore hypothesized that despite appropriate β-cell compensation (reflected by a constant DI), glucose increases when *M* decreases. We used a mathematical separation of changes in DI and changes along the hyperbola, with DI remaining constant, to analyze cross-sectional, longitudinal, and prospective data of insulin secretion and action in Pima Indians and Caucasians with NGT.

RESEARCH DESIGN AND METHODS

Based on availability of hyperinsulinemic-euglycemic clamps and intravenous glucose tolerance tests (IVGTTs) performed as part of the same study, 413 Pima Indians with NGT (7) were included in the cross-sectional and prospective analysis. Of these, 62 developed diabetes after a mean follow-up of ~5 years, while the rest maintained NGT. For the longitudinal analysis, data from 187 Pima Indians with NGT at baseline and at follow-up were available. Subjects had participated in ongoing studies of the pathogenesis of type 2 diabetes and were between 18 and 45 years of age, nonsmokers at the time of the study, and healthy according to a physical examination and routine laboratory tests. The characterstics of the groups are shown in Table 1. We also performed the cross-sectional analyses in 60 Caucasians with NGT.

Subjects were admitted for 8–10 days to the National Institutes of Health Clinical Research Unit in Phoenix, Arizona, where they were fed a weight-maintaining diet (50% of calories as carbohydrate, 30% as fat, and 20% as protein) and abstained from strenuous exercise. After at least 3 days on the diet, subjects underwent a series of tests for the assessment of body composition, glucose tolerance, *M*, and β-cell function. The protocol was approved by the Tribal Council of the Gila River Indian Community and the Institutional Review Board of the National Institute of Diabetes and Digestive

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AIR, acute insulin response; BCDI, β-cell demand index; CIR, corrected insulin response; DI, disposition index; IVGTT, intravenous glucose tolerance tests; *M*, insulin action; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

TABLE 1
Subject characteristics: cross-sectional, longitudinal, and prospective analyses

	Pima Indians, cross-sectional (and prospective) analysis	Caucasians, cross-sectional analysis	Pima Indians, longitudinal analysis	
			Baseline	Follow-up
n (M/F)	413 (267/146)	60 (36/24)	187 (131/56)	
Age (years)	26.7 ± 0.3 (18.2–44.0)	28.6 ± 0.9 (18.8–44.0)	25.9 ± 0.4	30.1 ± 0.5
Body fat (%)	31.0 ± 0.4 (9.2–50.1)	28.0 ± 1.4 (6.0–45.3)	30.4 ± 0.6	32.4 ± 0.6
BMI (kg/m^2)	32.8 ± 0.4 (19.0–81.7)	31.7 ± 1.0 (18.2–53.0)	33.2 ± 0.6	35.2 ± 0.6
Fasting glucose (mg/dl)	88 ± 0.4 (55–119)	90 ± 1 (73–110)	90 ± 1	89 ± 1
2-h glucose (mg/dl)	109 ± 1 (51–139)	106 ± 2 (60–137)	109 ± 1	111 ± 1
Fasting insulin (μU/ml)	37 ± 0.9 (5–124)	24 ± 1 (8–53)	34 ± 1	40 ± 1
2-h insulin (μU/ml)	149 ± 5 (16–904)	97 ± 13 (15–689)	138 ± 7	165 ± 8
M (mg/kg EMBS/min)	2.82 ± 0.05 (1.32–8.9)	3.8 ± 0.2 (2.1–7.9)	2.89 ± 0.09	2.63 ± 0.06
AIR (μU/ml)	249 ± 8 (28–1253)	133 ± 11 (16–430)	265 ± 13	267 ± 13

Data are mean ± SE (range).

and Kidney Diseases, and all subjects provided written informed consent before participation.

Oral glucose tolerance test (OGTT) and analytic procedures. After a 12-h overnight fast, subjects underwent a 75-g OGTT for assessment of glucose tolerance according to the 1985 World Health Organization diagnostic criteria (7). Plasma insulin concentrations were determined by an automated immunoassay (Access; Beckman Coulter). Insulin secretory function was estimated from the OGTT using the corrected insulin response (CIR), calculated as $\text{insulin}_{30\ \text{min}}/[\text{glucose}_{30\ \text{min}} \times (\text{glucose}_{30\ \text{min}} - 70)]$, as previously described and validated in Pima Indians (8).

Hyperinsulinemic-euglycemic glucose clamp. *M* was assessed during a hyperinsulinemic-euglycemic glucose clamp (100 min, insulin infusion rate of 240 nmol · m^2 body surface area^{-1} · min^{-1}), as previously described (9). The rate of total insulin-stimulated glucose disposal was calculated for the last 40 min after correction for endogenous glucose output, adjustment for steady-state plasma glucose and insulin concentrations, and normalization to estimated metabolic body size (fat-free mass − 17.7 kg).

IVGTT. Insulin secretion was measured in response to a 25-g intravenous glucose bolus injected over 3 min. The acute insulin response (AIR) to intravenous glucose was calculated as the average incremental plasma insulin concentration from 3 to 5 min after the glucose bolus (10).

Calculations. The surface plot of glycemia (both fasting and 2-h glucose concentrations) as a function of *M* and insulin secretion (AIR) gives a three-dimensional impression of the effects of deviation along the hyperbola on glycemia (Fig. 1). For generating the surface plot, the variability of the individual data had to be reduced and *M* and AIR values were categorized (see Fig. 1 legend).

For a continuous and mathematically correct treatment of the data points in the AIR by *M* representation (Fig. 2*A*), it was neessary to define a component along the hyperbola (Fig. 2*C*) and one orthogonal to the hyperbola (Fig. 2*B*). The latter is quantitated by the DI, calculated as the product of AIR and *M* as originally proposed (4). It measures adequacy of compensation of AIR in response to change in *M*.

The component along the hyperbola (or along any hyperbola) is quantitated by the ratio of AIR divided by *M*, which we have called the β-cell demand index (BCDI). It reflects the compensatory load imposed on AIR by any decrease in *M*. The hyperbolic relationship can be linearized by logarithmic transformation of *M*, AIR, DI, and BCDI, resulting in truly orthogonal variability between DI and BCDI (Fig. 2*D*). Use of these two indices in general linear regression models allowed us to adjust the effect of one index for the effect of the other index. In a similar fashion, a DI and BCDI were calculated using the CIR from the OGTT instead of AIR.

Statistical analyses. Statistical analyses were performed using software from the SAS Institute (Cary, NC). Data are given as mean ± SE. *M*, AIR, DI, and BCDI were logarithmically transformed. General linear regression models were used to assess independent influences of the variables entered. A P value <0.05 was considered to indicate statistical significance.

In the cross-sectional analyses, the relationship between the BCDI and both fasting and 2-h plasma glucose concentrations independent of DI was examined. In the longitudinal analyses, the change in plasma glucose as function of change in BCDI was assessed after adjusting for baseline plasma glucose, baseline DI, baseline BCDI, change in DI, and time of follow-up. In the prospective analyses, we examined whether DI and BCDI were independent risk factors for progression from NGT to diabetes using proportional hazard analysis. The results of three different models, including age, sex, and percent body fat, are presented. The effects of DI and BCDI were expressed as relative hazards with 95% CIs. For the purpose of presentation, the relative estimates were scaled for comparison at the 10th and 90th percentiles, i.e., risk of developing diabetes of a hypothetical subject at the 90th versus one at the 10th percentile.

RESULTS

Cross-sectional analysis. Figure 1 illustrates the three-dimensional relationship among *M*, insulin secretion (AIR), and glycemia (fasting and 2-h glucose concentration). AIR and *M* have been log transformed to linearize

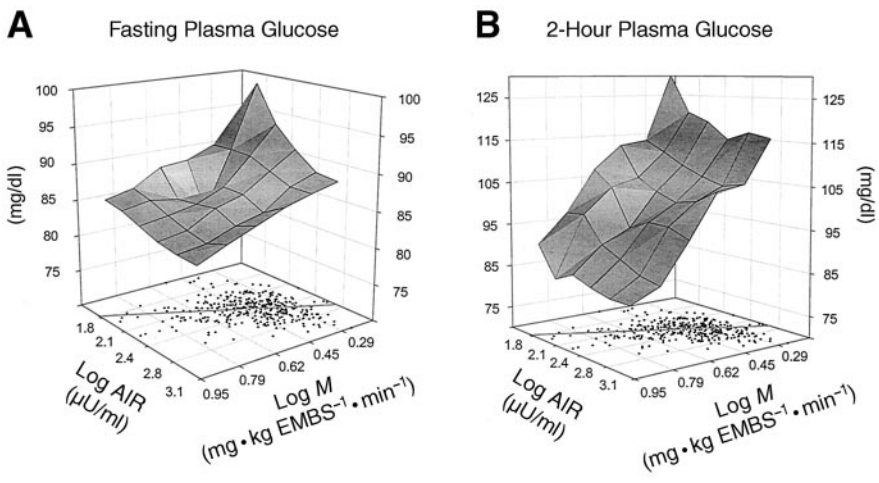

FIG. 1. Three-dimensional relationship among the AIR (log AIR) from the IVGTT, *M* (log *M*) from the hyperinsulinemic-euglycemic clamp, and glycemia. Fasting glucose concentrations (*A*) and 2-h glucose concentrations (*B*) during an OGTT in 413 Pima Indians. The 5-by-5 grid was generated by dividing both log AIR and log *M* into five equal intervals. The mean plasma glucose concentration of the subjects contained in one square was used to construct the mesh graph. The three-dimensional mesh was interpolated using the inverse distance method on 21 xyz data points (nonempty squares) with weight paramter 3 and 5 intervals (SigmaPlot; SPSS, Richmond, CA). In the xy-plain, the linear least square regression line of the correlation between log *M* and log AIR is shown. Both panels show that glycemia increases when *M* decreases, even if AIR increases (i.e., the projection of the regression line onto the mesh has a slope significantly different from zero).

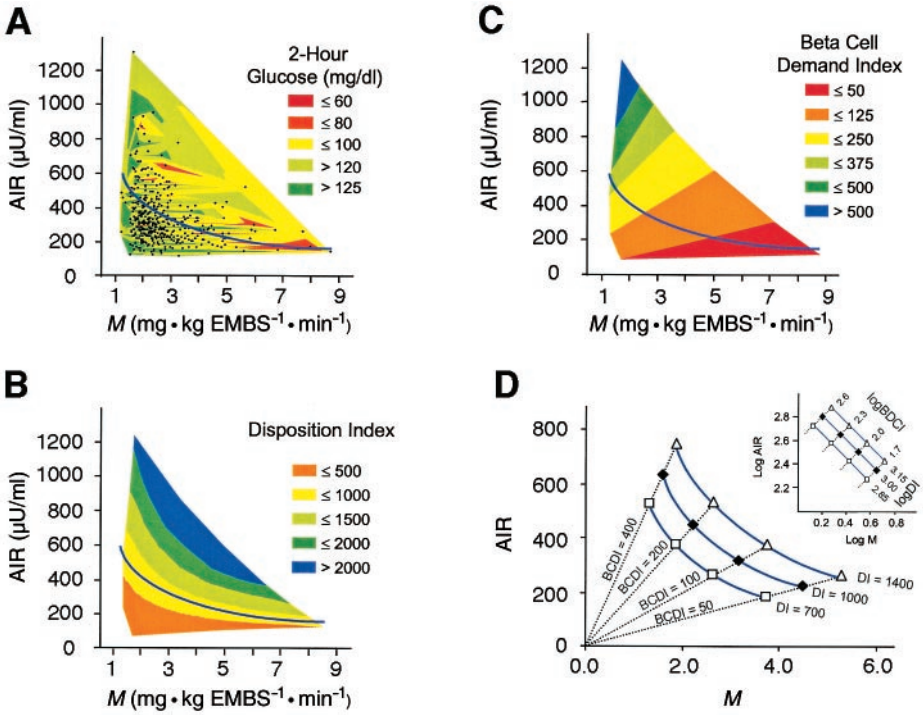

FIG. 2. Hyperbolic relationship between the AIR from the IVGTT and *M* from the hyperinsulinemic-euglycemic clamp. *A*: 2-h plasma glucose concentrations (OGTT) color-coded in 413 Pima Indians with NGT. Moving left and up on the hyperbola is associated with increasing 2-h plasma glucose concentrations. *B*: The DI (AIR × *M*) of the 413 individuals is color-coded. *C*: The BCDI (AIR/*M*) of the 413 individuals is color-coded. *D*: Data simulation for 12 theoretical individuals using four values for BCDI and three values for DI. The insert using the same data after log transformation illustrates the concept of BCDI quantifying variability orthogonal to the variability in DI.

the relationship (the hyperbola becomes a straight line). As expected, a decrease in both *M* and AIR (i.e., going from orange to blue in Fig. 2*B*) results in a pronounced increase in glycemia, essentially reflecting the decrease in DI. Interestingly, going along the other diagonal line (i.e., from red to blue in Fig. 2*C*) is also accompanied by an increase in glycemia. Clearly, both fasting and postprandial glycemia were higher with low *M* and high AIR than with high *M* and low AIR.

Figure 2 illustrates the development of the mathematical modeling of the relationships between AIR and *M*. The original hyperbolic relationship between insulin secretion and *M* in 413 Pima Indians with NGT is shown in Fig. 2*A*. The values of 2-h plasma glucose concentration (OGTT), DI, and BCDI are color-coded within the AIR-by-*M* representation (Fig. 2*A*–*C*). Figures 2*B* and *C* show that the variation in BCDI is exactly orthogonal to the variation in DI. This becomes particularly obvious in the logarithmically transformed insert of Fig. 2*D* using simulated data. Thus, use of the BCDI allowed us to quantify increase in insulin secretion per decrease in *M* for any given DI.

BCDI and DI were positively correlated ($R = 0.57$, $P < 0.0001$). Adjusting one for the other (equivalent to calculating the residuals) permitted assessment of independent relationships with glycemia. DI adjusted for BCDI was correlated with both fasting ($R = -0.28$, $P < 0.0001$) and 2-h plasma glucose concentration ($R = -0.32$, $P < 0.0001$). BCDI adjusted for DI was also correlated with both fasting ($R = 0.23$, $P < 0.0001$) and 2-h plasma glucose concentration ($R = 0.21$, $P < 0.0001$) (Fig. 3*A*). In Caucasians, adjusted BCDI also correlated positively with both fasting ($R = 0.27$, $P = 0.03$) and 2-h plasma glucose concentration ($R = 0.39$, $P = 0.002$). In a subgroup of Pima Indians who did not develop diabetes within ~5 years ($n = 351$), BCDI adjusted for DI was still positively correlated with both fasting ($R = 0.20$, $P < 0.0001$) and 2-h plasma glucose concentration ($R = 0.21$, $P < 0.0001$). Finally, using CIR as a measure of insulin secretion from the OGTT, BCDI adjusted for DI was also correlated with both fasting ($R = 0.20$, $P < 0.0001$) and 2-h plasma glucose concentration ($R = 0.16$, $P = 0.0003$).

Longitudinal analysis. In the longitudinal analysis, changes in BCDI were correlated with changes in fasting plasma glucose concentrations ($R = 0.19$, $P = 0.009$) and changes in 2-h plasma glucose concentrations ($R = 0.14$, $P = 0.04$). The models were adjusted for baseline glucose, baseline DI (log), baseline BCDI (log), changes in DI (log), and time of follow-up as covariates. To graphically illustrate how changes in *M* and compensatory changes in AIR relate to changes in glucose independent of changes in DI, we used the adjusted changes in BCDI to form four groups: two with decreasing adjusted BCDI and two with increasing adjusted BCDI (by deciles of change). It is important to note that DI at baseline and follow-up was remarkably similar between the four groups (Table 2). Figure 3*B* illustrates the changes in both fasting and 2-h plasma glucose concentrations associated with deviations along a constant mean DI of ~500. For example, in the group with the highest increase in BCDI, the mean 2-h plasma glucose concentration increased by 16 mg/dl. In the group with the lowest decrease in BCDI, the mean 2-h plasma glucose concentration decreased by 20 mg/dl.

Prospective analysis. Prospectively, risk of type 2 diabetes was independently associated with low DI and high BCDI (model 1, Table 3). This association remained statistically significant upon inclusion of percent body fat, age, and sex (models 2 and 3, Table 3).

DISCUSSION

The relationship between insulin secretion and *M* in both Pimas and Caucasians was approximated by a hyperbolic function. This essentially reflects β-cell compensation for insulin resistance. We tested the hypothesis that despite a

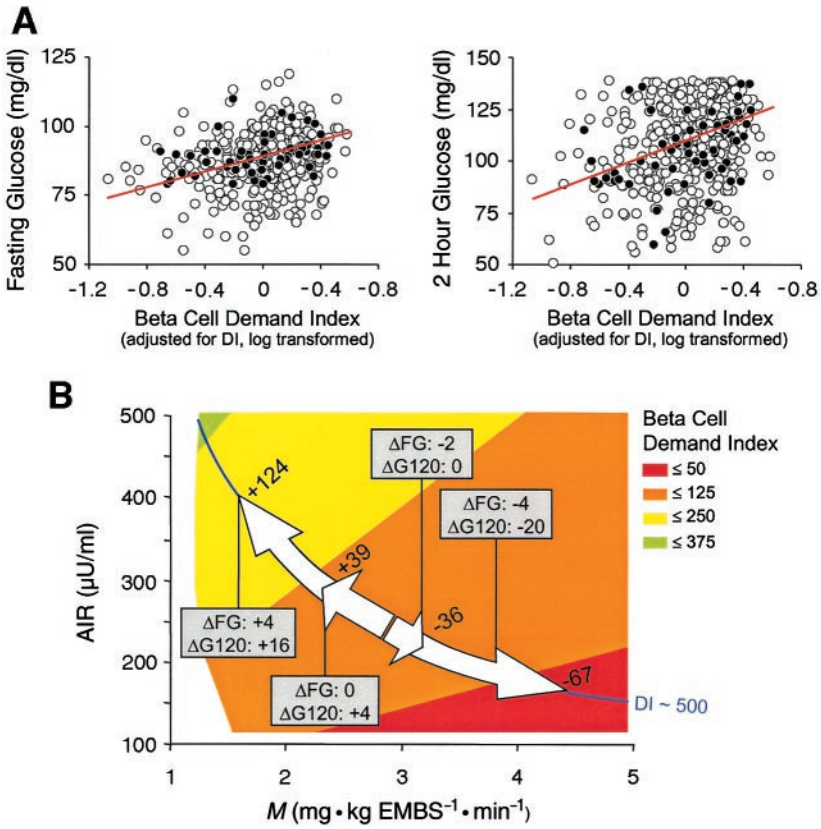

FIG. 3. Results of the cross-sectional and longitudinal analyses. *A*: Cross-sectional correlations between log BCDI adjusted for log DI and fasting plasma glucose concentration ($r = 0.27$, $P < 0.0001$, left panel) and 2-h plasma glucose concentration ($r = 0.31$, $P < 0.0001$, right panel), respectively (○, Pima Indians, $n = 413$; ●, Caucasians, $n = 60$). The red line represents the linear least square regression line. *B*: Longitudinal changes in glycemia associated with changes in BCDI while maintaining a constant DI in 187 Pima Indians who were normal glucose tolerant at baseline and follow-up. Four groups were formed based on deciles of change in BCDI adjusted for baseline glucose, baseline DI, baseline BCDI, changes in DI, and time of follow-up: the short arrows represent the lowest nine deciles of change, while the long arrows represent the highest deciles of change. The change in glycemia (fasting glucose [FG] concentration and 2-h glucose concentration [G120]) resulting from the change in BCDI in the four groups (numerals along the hyperbola) is shown in the boxes. The long arrows clearly demonstrate that movement along the hyperbola can be accompanied by a substantial change in glycemia.

constant DI, glycemia increases when *M* decreases. A constant DI is thought to reflect the appropriateness of β-cell compensation for insulin resistance.

Use of the BCDI allowed us to separate deviation along the hyperbola from deviation from the hyperbola. Cross-sectionally, in both Pima Indians and Caucasians, BCDI adjusted for DI was positively associated with glycemia, suggesting that even for a constant DI, the compensation regarding glucose is incomplete. This was independently confirmed by the longitudinal analyses, which actually measures changes over time that are often only inferred from cross-sectional data. In people with increasing BCDI,

TABLE 2
Longitudinal analysis: subgroups categorized according to deciles of change in BCDI (adjusted) (Pima Indians, $n = 187$)

	Increase in BCDI		Decrease in BCDI		
	Highest decile	Lower nine deciles	Highest decile	Lower nine deciles	*P* (ANOVA)
n	8	88	8	83	
Change BCDI (log, adjusted*)	0.37 ± 0.02	0.13 ± 0.01	−0.40 ± 0.03	−0.13 ± 0.01	<0.0001
Follow-up time (years)	4.8 ± 0.9	4.3 ± 0.3	4.7 ± 1.0	4.0 ± 0.3	0.8
BCDI					
Baseline	80 ± 17	113 ± 10	112 ± 35	114 ± 12	0.8
Follow-up	204 ± 20	152 ± 11	45 ± 9	78 ± 6	<0.0001
DI					
Baseline	722 ± 132	701 ± 41	704 ± 132	682 ± 43	1.0
Follow-up	100 ± 13	103 ± 7	112 ± 13	96 ± 6	0.8
Fasting glucose (mg/dl)					
Baseline	91 ± 2	90 ± 1	87 ± 2	90 ± 1	0.6
Follow-up	94 ± 2	90 ± 1	82 ± 2	88 ± 1	0.003
2-h glucose (mg/dl)					
Baseline	99 ± 7	110 ± 2	104 ± 7	110 ± 2	0.4
Follow-up	115 ± 5	114 ± 2	84 ± 6	110 ± 2	<0.001
AIR (pmol/l)					
Baseline	230 ± 42	269 ± 18	268 ± 62	265 ± 22	1.0
Follow-up	374 ± 33	316 ± 22	180 ± 25	214 ± 14	<0.001
M (mg · kg EMBS^{-1} · min^{-1})					
Baseline	3.2 ± 0.4	2.8 ± 0.1	2.9 ± 0.4	2.9 ± 0.1	0.8
Follow-up	1.9 ± 0.1	2.2 ± 0.04	4.4 ± 0.3	3.0 ± 0.1	<0.0001

Data are mean ± SE.

TABLE 3
Proportional hazard analysis: risk predictors for type 2 diabetes in different models (Pima Indians, NGT at baseline, $n = 413$; conversion to diabetes events, $n = 62$)

	Odds ratio 95% confidence limits	P
Model 1		
Log BCDI	5.67 (2.13–15.10)	<0.001
Log DI	0.07 (0.03–0.18)	<0.001
Model 2		
Percent body fat	1.04 (1.00–1.07)	0.046
Log BCDI	3.94 (1.36–11.48)	0.01
Log DI	0.09 (0.04–0.25)	<0.001
Model 3		
Age	0.98 (0.94–1.02)	0.36
Sex	0.57 (0.29–1.13)	0.11
Percent body fat	3.59 (1.33–9.62)	0.01
Log BCDI	3.13 (1.03–9.53)	0.04
Log DI	0.09 (0.03–0.25)	<0.001

glycemia increased (and vice versa) over a wide range of almost 10 mg/dl for fasting and 40 mg/dl for 2-h plasma glucose concentrations in the extreme groups (Fig. 3*B*). In prospective analyses, subjects with higher BCDI at baseline were more likely to reach the threshold for the diagnosis "diabetes" than those with a lower BCDI. In summary, the three analyses demonstrated that an increase in BCDI (indicating movement left and upward on the hyperbola) (Figs. 2*A* and 3*B*) is associated with an increase in glycemia (and vice versa) and that these higher glucoses are associated with an increased risk of diabetes. These data clearly challenge the commonly held view that in subjects with NGT the compensatory increase in β-cell function in response to insulin resistance maintains glucose constant.

The data are also consistent with the hypothesis that glucose is one of the signals driving the compensatory increase in β-cell function. If that is the case, the increase in glycemia represents a feed-forward system in which the stimulus (increased glucose) for the compensation (increased AIR) must remain in place as long as the primary perturbation (insulin resistance) is present. Thus, with respect to glucose concentrations, β-cell compensation has to be incomplete. If β-cell compensation were "complete" and caused glycemia to return to where it started (before *M* decreased), the stimulus that drove up insulin secretion would be removed and with it the increase in insulin secretion. Consequently, there would be no compensation at all.

This feed-forward principle can be visualized using the fluid model illustrated in Fig. 4 (see also legend). Clearly, as long as the perturbation (insulin resistance) remains active, the system cannot permit glucose concentration to return to where it started to keep the compensation going. Any acute and transient perturbations of the system can also be explained. A meal, for example, would cause a transient increase in inflow of glucose into the sink, followed by an increase in insulin secretion. The resulting increase in outflow represents appropriate adaptation, with everything returning to normal when the excess inflow ends.

It is necessary to point out that increased glycemia may not be the only signal to inform the β-cell of the presence

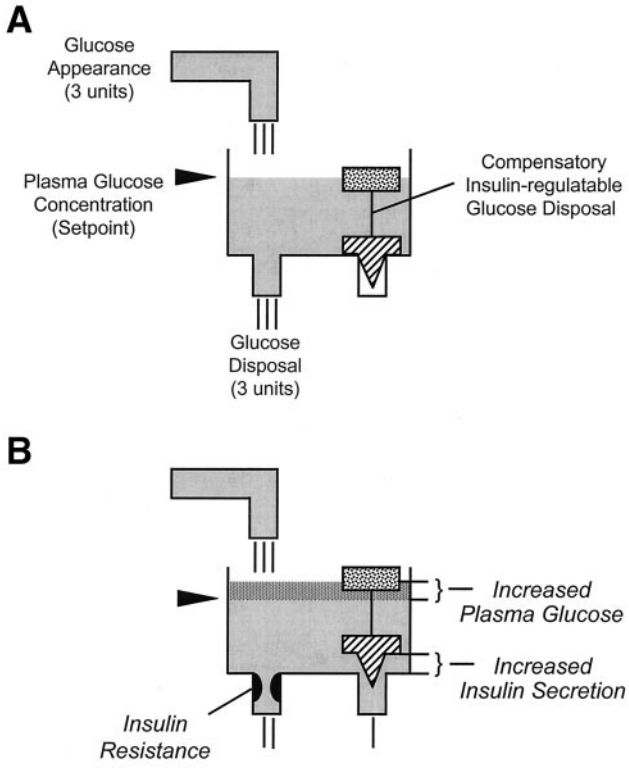

FIG. 4. Schematic representation of the feed-forward system: insulin resistance → increased glycemia → increased insulin secretion. At steady state, glucose appearance equals glucose disposal and glucose concentration remains unchanged. A fixed glucose concentration (liquid level) is assumed, representing the set stimulus for a given insulin secretion (level of the floating plug). *A*: Representing the normal state, the compensatory insulin-regulatory glucose disposal is not activated (closed plug). *B*: The "normal," fully compensated insulin-resistant state. Decreased glucose disposal results in an increased glucose concentration that in turn will cause the "floating plug" to rise (increased insulin secretion) and permit compensatory glucose disposal. This rise will continue until the total glucose disposal again equals glucose appearance. To secure continuous patency of the compensatory outlet, the glucose level must stay above the original set point level. A (theoretical) replugging of the compensatory outlet would instantaneously cause an increase in glucose concentration and therefore cannot happen as long as the obstruction due to insulin resistance is present.

of insulin resistance. Other possible stimuli for β-cell compensation in response to insulin resistance (and/or increased fatness) include glucagon-like peptide-1, acylation-stimulating protein, neural factors, and fatty acids (5). We do not have adequate data to confirm or refute any of those. Nevertheless, our findings argue in favor of the notion that chronic increases in glycemia, even mild ones, are involved.

Previous studies in selected insulin-resistant groups may not have found a significant increase in glycemia (for example, in obese individuals with NGT [11]). However, these studies are limited by the small number of subjects and the cross-sectional design, which cannot assess the change in glycemia over time during the development of insulin resistance in a given individual. In support of our notion, in a longitudinal study in 60 children experiencing insulin resistance of puberty (from Tanner I to III), fasting glucose increased on average 3.5 mg/dl (12).

What are the implications of these findings (and interpretations) regarding physiology versus pathophysiology? Disregard for a moment that decreasing insulin sensitivity

(for whatever reason) most probably represents a pathophysiological process in itself. The data indicate that the increase in glycemia (within the so-called normoglycemic range), at least in part, contributes to the compensatory increase in insulin secretion rather than resulting from a lack of it. Thus, provided the DI remains unchanged, the increase in glycemia accompanying the compensatory increase in insulin secretion appears to be a normal physiologic process. Studies in β-cells suggest that mild hyperglycemia actually lowers the glucose set point for insulin secretion at any glucose level. This is believed to be secondary to upregulation of hexokinase activity relative to glucokinase acitvity (13) and would explain the increased responsiveness of insulin secretion with mildly increased glycemia.

It is worth considering, however, whether a chronic mild-to-moderate increase in glycemia can have biologically detrimental consequences. Higher glucose concentrations, even within the normal range, are associated with an increased risk of diabetes, as shown here and many times previously (reviewed and meta-analyzed in 14). Of greater importance, perhaps, is the association of mild increases in glycemia with increased all-cause mortality. In the largest of such studies, in >16,000 healthy men, a 2-h postload plasma glucose concentration of 107 mg/dl was associated with a 15% increase in all-cause mortality, as compared with 98 mg/dl (15). The biochemical mechanism(s) of these associations is not known but worthy of thorough investigation and might have important public health implications.

We felt that the term "glucose homeostasis" imprecisely describes the physiologic situation where chronic insulin resistance causes increased glycemia. In 1988, Sterling and Eyer (16) introduced the term "allostasis" as an essential component of maintaining health in response to stress. The concept became a general principle in biology and biomedicine to explain how changes throughout life sustain the ability to acutely battle challenges at some cumulative cost to system resources (17–19).

The term glucose homeostasis (literally, stability through staying the same) describes a system that is essential for life and becomes operative when an acute and transient stressor (e.g., oral glucose load) is introduced. Sequentially, glucose concentration increases, insulin secretion increases, glucose disposal is stimulated, and, finally, glucose concentration returns to where it started. A chronic, relatively hyperglycemic state is prevented. When the stressor is chronic (i.e., insulin resistance due to obesity), the process becomes allostatic (literally, stable through change) to maintain homeostasis. During glucose allostasis as a consequence of insulin resistance, glucose fails to return to the concentration that was present before the chronic stressor was introduced. This higher glycemia is necessary to continuously inform the β-cell that insulin resistance is present. It will thus ensure the homeostatic response to the next glucose load, i.e., a greater insulin secretory response, but may become damaging over time and when glycemia exceeds a certain threshold.

In conclusion, the cross-sectional, longitudinal, and prospective data from Pima Indians and Caucasians are consistent with the hypothesis that glucose is a signal that stimulates AIR to compensate for insulin resistance. This compensation, as in any feed-forward system, is incomplete with respect to normalizing glycemia so as not to eliminate the stimulus responsible for the compensation. The process becomes chronically allostatic to remain acutely homeostatic. Over time, this normal physiologic response may well have pathophysiologic consequences, such as the development of type 2 diabetes. The consequence for clinical practice is that any decrease in insulin sensitivity comes with an increase in glycemia.

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