

**Degree of obesity and glucose allostasis are major effectors of glucose tolerance dynamics
in obese youth**

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Abstract

Objective: One of the signals for the beta cell to maintain an adequate response to worsening insulin sensitivity is elevated ambient glycemia, namely the concept of “glucose allostasis”. We examined whether the “glucose allostasis” can be demonstrated using oral glucose tolerance tests and the effects of the dynamics of beta cell demand on longitudinal changes of glucose tolerance in obese youth.

Design and methods: A cross sectional analysis of 784 oral glucose tolerance tests of obese youth was used to demonstrate the concept of allostasis and a longitudinal assessment of 181 subjects was used to examine the effects of changes in beta cell demand and degree of obesity on glucose tolerance.

Results: “Glucose allostasis” can be demonstrated using indices derived from an oral glucose tolerance test. Increasing beta cell demand and the degree of obesity at baseline were independently related to elevations in ambient glycemia over time. Baseline BMI Z score was a significant contributor to elevated glucose levels on the second OGTT while the change in degree of obesity during the follow up was not.

Conclusions: Increasing beta cell demand related to worsening insulin sensitivity and the degree of obesity per se have independent roles in the development of elevated glucose levels over time. This implicates that peripheral insulin sensitization and / or beta cell enhancement alongside a significant reduction in obesity may be needed to prevent the development of altered glucose metabolism in obese youth.

The relation of insulin sensitivity and secretion is described as a hyperbola, thus when insulin sensitivity is decreased, an increase in insulin secretion is required to maintain euglycemia (1). This relation has been described as “the disposition index” and reflects the β cell adaptation potential to worsening insulin resistance (2). The concept of the disposition index views the β cell as a responsive organ to stimuli generated by insulin target organs such as muscle, liver or fat. There are several potential candidates that may signal the β cell regarding ambient insulin sensitivity, one of which is obviously glucose. If glucose is a peripheral signal for the β cell to increase insulin secretion, levels of glycemia must rise in order to provide a continuous stimulus for the generation of this compensation. This phenomenon is termed “glucose allostasis” and has been elegantly described by Stumvoll et al (3) using clamps in adults.

The prevalence of obesity in childhood has risen significantly recently (4) together with the rise in the prevalence of type 2 diabetes (T2DM) in youth, thus they are described as the “twin epidemics” (5). The rapid tempo at which T2DM develops in obese children raises questions regarding a potential impact of obesity per se in the underlying pathophysiology of the disease, in comparison to adults. Potential candidates that can link obesity and altered glucose metabolism, independent of effects on insulin sensitivity, include elevated free fatty acids, fat derived inflammatory cytokines and low adiponectin levels, that might all mediate accelerated beta cell failure.

We have previously shown that the oral glucose tolerance test (OGTT) can be used to demonstrate the hyperbolic relation of insulin sensitivity and secretion in obese children and adolescents (6). The aims of this study were: 1) to demonstrate the concept of glucose allostasis using a cross sectional cohort of obese children and adolescents who

performed OGTTs; 2) to study the effects of changes in beta cell demand and obesity status over time on glucose levels using a longitudinal cohort of obese children and adolescents who repeated their OGTT. We postulated based on our preliminary findings (7) that an increased degree of obesity and continuous weight gain will have an independent effect on levels of glycemia during the longitudinal follow up, independent of changes in insulin sensitivity and/or beta cell demand.

Subjects and Methods

Participants in this cohort were recruited to perform an OGTT from the Yale Pediatric Obesity Clinic as part of a study of the pathophysiology of T2DM in youth. Some of these subjects have been described in previous publications (7, 8). All participants were between the ages of 4 to 18 years. All underwent a physical examination that included anthropometric determinations and pubertal status (9) and were classified as pre-pubertal or pubertal. Subjects with overt T2DM at baseline and those with medical conditions or using medications that may affect glucose metabolism were excluded from the study. All subjects had a body-mass index that was greater than the 95th percentile for age and gender and were thus classified as obese. In order to standardize the BMI levels, conversion to BMI z scores was performed based on the CDC growth charts (10). Participants were followed bi-annually as outpatients by the clinical staff and received nutritional guidance as well as recommendations for physical activity, as previously described (11). All participants of this cohort are encouraged to return to repeat their OGTT within ~ 18 months. Data from the 784 obese children and adolescents who had a baseline OGTT were analyzed for the cross sectional analysis and data from the subset of 181 participants who performed a second OGTT was used for the longitudinal

analysis. The mean follow up interval was 22 ± 12 months. Anthropometric and metabolic characteristics of the baseline cross sectional cohort and the subset that has a second OGTT were comparable (Table 1). The protocol was approved by the institutional review board of the Yale University School of Medicine. Written informed consent was obtained from the parents and assent from the children and adolescents.

Oral Glucose Tolerance test

Subjects were studied at the Yale Children's Clinical Research Center at 8 a.m. after a 12-hour overnight fast as previously described (7, 8). Two base-line samples were then obtained for measurements of plasma glucose, insulin, C-peptide and lipids. Thereafter, flavored glucose (Orangedex, Custom Laboratories, Baltimore) in a dose of 1.75 g per kilogram of body weight (up to a maximum of 75 g) was given orally, and blood samples were obtained every 30 minutes for 180 minutes for the measurement of plasma glucose, insulin, and C-peptide.

Biochemical Analysis

Plasma glucose level was determined with YSI 2700 STAT Analyzer (Yellow Springs Instruments). Plasma insulin was measured with a radioimmunoassay made by Linco (St. Charles, Mo.), which has less than 1 percent cross-reactivity with C-peptide and proinsulin. Plasma C-peptide levels were determined with an assay made by Diagnostic Product (Los Angeles). The intraassay variation was 11 percent for insulin and 13 percent for C peptide and the interassay variation was 12 percent for insulin and 12 percent for C peptide

Calculations

The insulinogenic index (IGI), calculated as the ratio of the increments in insulin and glucose levels during the first 30 minutes after the ingestion of glucose, was

used to assess early beta-cell response (12). Insulin sensitivity was determined by the Whole Body Insulin Sensitivity Index (WBISI, the Matsuda index) (13). The disposition index (DI) was calculated as the product of IGI and the square root of WBISI, based on the curvilinear relation of these OGTT derived indices, as previously described (6). To evaluate a component along the DI hyperbola, we followed the approach of Stumvoll et al (3) and calculated the ratio of the IGI and WBISI to derive the β cell demand index (BCDI). This index represents the additional burden placed on the β cell in the face of a decrease in insulin sensitivity while maintaining a constant DI. As shown in figure 1, for a given disposition index, the beta cell demand index (BCDI) rises as insulin sensitivity decreases and may be used to estimate the metabolic burden placed on the beta cell in order to provide adequate compensation.

Statistical analysis

Data are presented as means \pm standard deviation. Parameters that did not have a normal distribution were log transformed for the analysis. Adjustment for comparisons for potential confounders was performed using analysis of covariance using the general linear model procedure. Adjustment for multiple comparisons was performed using the Bonferonni procedure. Division of the cohort for the cross sectional analysis to quartiles of IGI, WBISI, DI and BCDI was based on the 25th, 50th and 75th percentile of these parameters for presentation purposes. Adjustments were made for age, gender, ethnicity and BMI-z score. For the longitudinal analysis we similarly divided the cohort to four categories of changes in BCDI by initially dividing the cohort to those who had a positive or negative change and then dividing these two groups using the median of each one. Thus, the BCDI change categories reflect the direction (positive or negative) and

the magnitude (large or small) of BCDI change. Baseline BMI Z score was divided into equal quartiles based on corresponding percentiles in order to evaluate the impact of baseline degree of obesity on later glycemic levels, independent of dynamics of insulin sensitivity, secretion and their inter-relations. An $\alpha < 0.05$ was considered statistically significant. All analyses were performed using SPSS 12.0 for Windows.

Results

Relation of fasting and 2-hr glucose and quartiles on insulin sensitivity and secretion

Cross sectional analysis

The relations of the 2-hr glucose, fasting glucose and quartiles of IGI and WBISI are shown in figure 2 (see online appendix at <http://care.diabetesjournals.org>). The effect of IGI and of WBISI quartiles on 2-hr glucose was significant ($p < 0.001$) while the interaction between them was not (implying that they are independent and additive but not synergistic). These effects remained statistically significant after adjustment for age, gender, ethnicity, pubertal status and BMI-z score. Similarly, IGI and WBISI quartiles had significant effects on fasting glucose ($p < 0.001$) while the interaction between them did not. These effects remained statistically significant after similar adjustments, although interestingly, gender had a significant effect in this model ($p < 0.001$) with males having a greater fasting glucose compared to females (92 vs. 89 mg/dl, $p < 0.001$).

Relation of fasting and 2-hr glucose and quartiles on disposition index and beta cell demand

Cross sectional analysis

The relations of the disposition index (DI) and the beta cell demand index (BCDI) and 2-hr and fasting glucose levels are shown in figure 3. The effects of DI and BCDI on 2-

hr glucose level were significant individually ($p < 0.001$) as was the interaction between them ($p < 0.001$) reflecting the concept of allostasis per se (ie, to maintain a constant DI in the face of worsening insulin sensitivity, the signal for the beta cell to compensate by adequate secretion of insulin is rising ambient glycemia). The significant interaction between the two implies a synergistic effect, ie per given insulin sensitivity – a lower DI implies a greater BCDI leading to an even greater glycemic signal in order to provide adequate compensation. These effects remained significant after adjustment for age, gender, ethnicity, pubertal status and BMI-z score. The effects of DI and BCDI on fasting glucose were significant ($p < 0.001$) yet the interaction between them was not ($p = 0.10$). After similar adjustment, the effects of DI and BCDI on fasting glucose remained highly significant. Gender again had a significant effect on fasting glucose (92 for males vs. 89 mg/dl for females, $p < 0.001$).

Effect of changes in β cell demand and obesity on changes in fasting and 2-hr glucose

Longitudinal analysis

In order to evaluate the impact of changes in the β cell demand index (BCDI) on glucose levels we modeled the changes in fasting and 2-hour glucose between baseline and follow up OGTTs, while adjusting for baseline DI, baseline BCDI, change in DI, baseline fasting glucose, age, gender, ethnicity, pubertal status, time between studies and baseline BMI z score. As shown in figure 4B, the upper quartile of BCDI change, which had the greatest increase of beta cell demand, had significantly greater 2-hr glucose level change on follow up compared to the first and second BCDI change categories, who had a reduction of beta cell demand ($p = 0.006$ and $p = 0.003$ respectively). Similarly, those in the upper category of BCDI change had a greater change in fasting glucose levels on follow up

compared to the first category ($p=0.02$). Baseline BMI Z, baseline BCDI and change in DI had a significant effect on 2-hr glucose in this model ($p=0.007$, $p=0.007$ and $p<0.001$ respectively). The most obese participants at baseline had significantly greater increases in 2-hr glucose on follow up compared to the other three quartiles (figure 4D). This difference remained significant after adjustment for age, gender, ethnicity, pubertal status, time between studies, baseline fasting glucose, BCDI and DI, changes in BCDI and DI. Interestingly, adding the change in obesity over time to the model, expressed as BMI Z change or as absolute weight change had no significant effect on the model and did not modify the significance of baseline BMI or BCDI change category. Baseline degree of obesity had no effect on follow up fasting glucose (Figure 4B).

Discussion

In the present analysis we used the OGTT to demonstrate the phenomenon of glucose allostasis, manifested as an increase in ambient glycemia in order to maintain a constant disposition index while insulin sensitivity is decreasing. The main findings of this analysis show that OGTT derived indices can indeed demonstrate the allostatic effect of rising ambient glycemia in the face of increased β cell demand. At least one of the signals for the β cell to increase insulin secretion is glucose which is mildly yet significantly elevated in order to provide a continuous stimulation to the pancreas. Our longitudinal analysis demonstrated that increasing β cell demand is independently related to elevations in ambient glycemia and that the degree of obesity at baseline has an adverse effect on follow up glucose levels, independent of dynamics of insulin sensitivity and β cell demand. Moreover, baseline BMI Z score was a significant contributor to elevated glucose levels on the second OGTT while the

change in degree of obesity during the follow up was not.

The emergence of T2DM in the pediatric age group has raised questions regarding the underlying pathophysiology of this condition in comparison to adults. The rapid tempo of the development of β cell failure in youth suggests that parameters less relevant in adults, such as hormonal changes of puberty, might accelerate this process. Our data clearly demonstrate that the phenomenon of glucose allostasis (14), previously described in adults, is similarly relevant in obese children and contributes to the development of hyperglycemia over time. Indeed, changes in the β cell demand index in this cohort were independently related to changes in fasting and 2-hr glucose levels. This phenomenon can be observed in puberty related hormonal changes in non-obese adolescents which is related to a $\sim 33\%$ decrease in insulin sensitivity and with a transient increase of 3.5 mg/dl in fasting glucose that probably returns to pre-pubertal levels upon reaching Tanner stage V (15). Obesity is the major cause of peripheral insulin resistance in childhood and is tightly related to the development of altered glucose metabolism (16). Indeed, the mean value of insulin sensitivity index (WBISI) in this large cohort was ~ 2.0 reflecting baseline insulin resistance. At this level of sensitivity, further small decreases of insulin sensitivity necessitate large changes of insulin secretion in order to maintain a constant DI, thus causing major increases in β cell demand due to the increasing slope of the DI hyperbola in that numerical range of WBISI (figure 1). In this scenario, adding a second element which further reduces insulin sensitivity such as pubertal hormonal changes (17) or exogenous glucocorticoids (18) might tip the balance toward extreme β cell demand that can no longer be compensated by the pancreas, leading to β cell failure and increased glucose levels.

The longitudinal assessment demonstrated that the degree of obesity at baseline had an effect on increased levels of fasting and 2-hr glucose levels during follow up. This effect was independent of changes in insulin sensitivity, baseline and changes of the DI and BCDI and importantly, more significant than changes in relative adiposity (BMI Z score change) or absolute weight over time. This finding suggests that fat derived factors may have an independent role in the development of deteriorating glucose tolerance that is not mediated by effects on insulin sensitivity and that those with severe obesity are a specifically high risk group for deteriorating glucose tolerance. Potential mediators of the adverse effects of severe obesity on beta cells include among others increased levels of leptin (19), free fatty acids (20), and TNF- α as well as reduced adiponectin (21). Elevated leptin (22), free fatty acids (23) and TNF- α (24) have all been shown to hamper insulin secretion while adiponectin seems to have protective effects on beta cells (25).

The major impact of the changes of β cell demand and of baseline degree of obesity over time on dynamics of fasting and post prandial glucose levels raises several therapeutic implications. Obviously, prevention of severe obesity should be in the frontline of all therapeutic interventions. In

the severely obese child, reduction of β cell demand through use of insulin sensitizers or increasing the early insulin response using secretagogues may be of benefit. Such therapies, as well as pharmacologic interventions directed at weight loss per se, may also have beneficial effects on circulating concentrations of adipocytokines that will further reduce the burden on the β cell. Indeed, targeting both β cell enhancement and weight reduction in combination may be superior to treating only one. Treatment of obesity related sub-clinical inflammation, regardless of weight loss, may provide another therapeutic target in this context (26).

In summary, increasing β cell demand related to worsening insulin sensitivity and the degree of obesity per se have independent roles in the development of elevated glucose levels over time. Elevation of glucose levels may be a normal physiological adaptation to create a signal for the β cell to face the increased demand (allostasis) and may be a consequence of the unique pro-inflammatory milieu characteristic of the severely obese child. This implicates that peripheral insulin sensitization and / or β cell enhancement alongside a significant reduction in obesity may be needed to prevent the development of altered glucose metabolism in obese youth.

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Table 1. Demographic and anthropometric parameters of participants (mean \pm SD)

	Cross sectional analysis	Longitudinal analysis	
		Baseline	Post
N	N=784	N=181	
Age (yrs)	12.9 \pm 2.9	12.5 \pm 2.9	14.2 \pm 2.7
Gender (M/F) %	321(40%)/463 (60%)	61 (33%)/120(67%)	
Ethnicity (Cau, AA, His)	329(42%)/245(31%)/210(27%)	80(44%)/55(30%)/46(26%)	
BMI (kg/m²)	35.86 \pm 7.75	35.33 \pm 6.99	37.26 \pm 8.03
BMI-Z score	2.42 \pm 0.38	2.41 \pm 0.42	2.35 \pm 0.50
Fasting Glucose (mg/dl)	90 \pm 6	91 \pm 7	92 \pm 8
Glucose 120 min (mg/dl)	117 \pm 22	124 \pm 28	119 \pm 28
Insulin Sensitivity (WBISI)	2.00 \pm 1.25	1.66 \pm 0.90	1.71 \pm 1.04
Early Insulin Response (IGI)	5.08 \pm 4.91	4.77 \pm 3.67	4.62 \pm 3.74

Legends for figures

Figure 1. Relation of OGTT derived indices of insulin secretion and sensitivity and their interactions. As shown, for a given disposition index (DI), as insulin sensitivity is lower, early insulin response is higher. This translates to a greater beta cell demand index (BCDI) reflecting the metabolic burden placed on the beta cell in order to maintain a constant DI and normal glucose homeostasis.

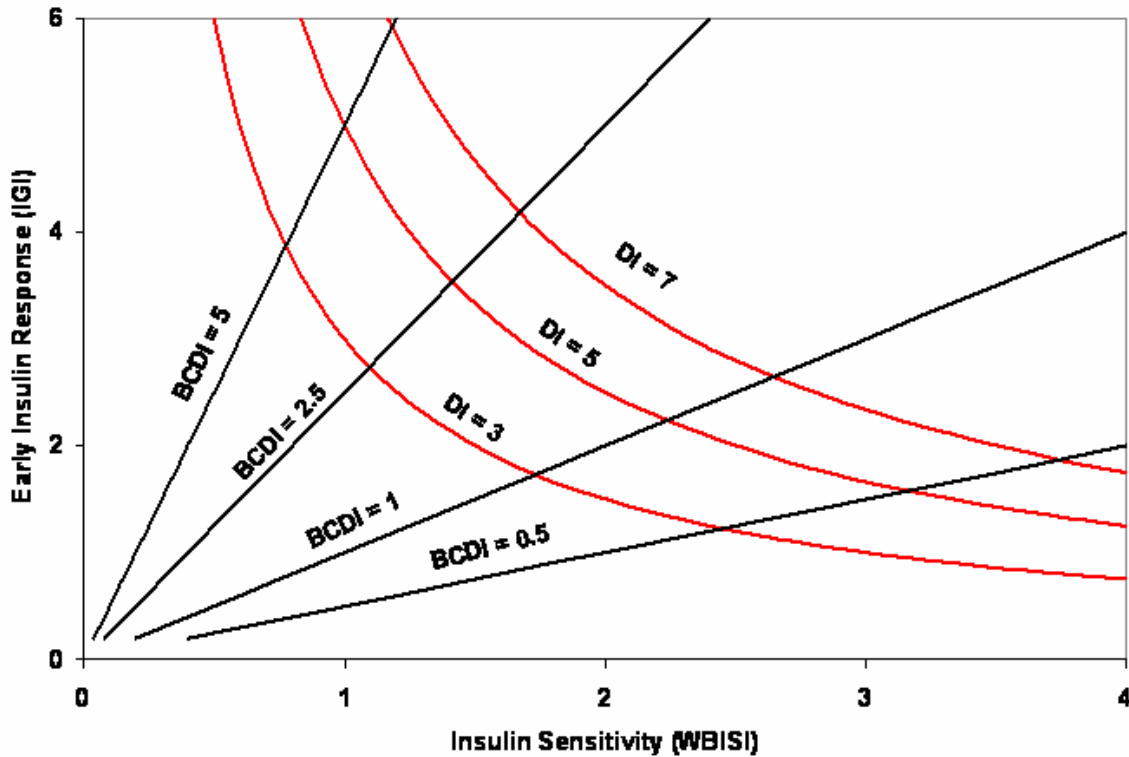


Figure 3. Relation of fasting glucose (left) and 2-hr glucose (right) and quartiles of the disposition index and the beta cell demand index (BCDI). Quartiles 1 of DI and of BCDI represent the subjects with the lowest disposition index and the lowest beta cell demand respectively. Per given DI, the greater the beta cell demand, the higher is fasting and 2-hr glucose ($p < 0.001$). Bars reflect means and error bars are SDs.

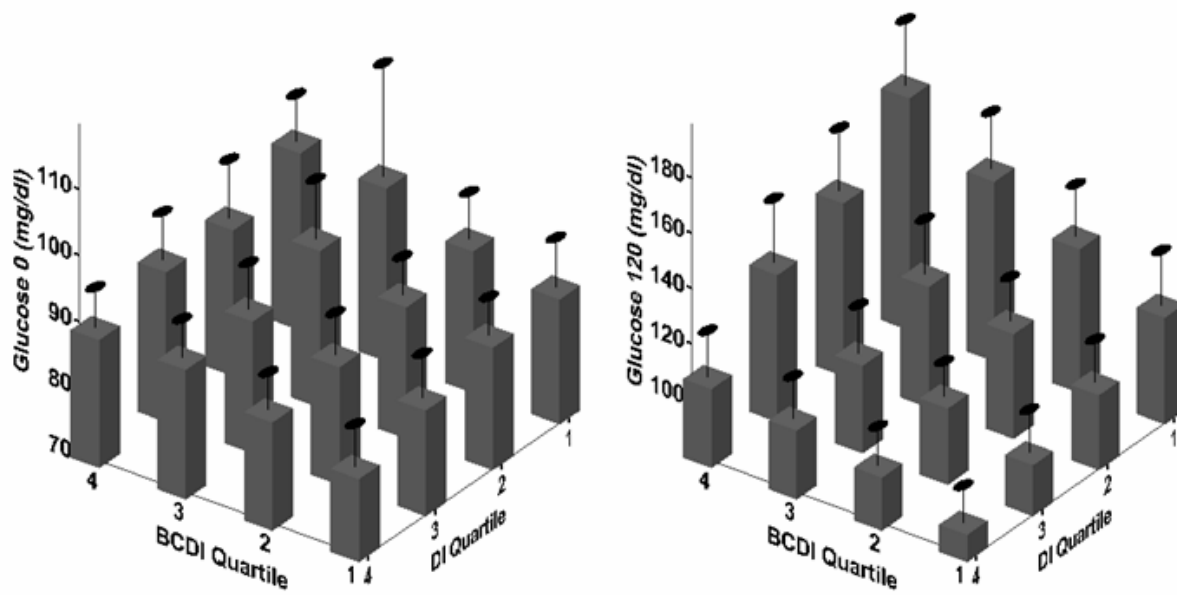


Figure 4. Adjusted effects of changes in beta cell demand index (BCDI) and baseline BMI Z score on changes in fasting (top) and 2-hr glucose (bottom).

Categories of BCDI change represent the following intervals: Category 1 : -1.76 - -0.33; category 2 : -0.32 - -0.01; category 3 : 0 - +0.24; category 4 : +0.25 - +1.38 (.categories 1 and 2 reduced their BCDI while categories 3 and 4 increased it).

Categories of baseline BMI Z score represent the following intervals: Category 1: 1.91 - 2.21; category 2: 2.23 - 2.46; category 3: 2.47 - 2.69; category 4: 2.70 - 3.28

