

ASSESSING THE RISK OF IMPAIRED GLUCOSE METABOLISM IN OVERWEIGHT ADOLESCENTS

ASSESSING THE RISK OF IMPAIRED GLUCOSE METABOLISM
IN OVERWEIGHT ADOLESCENTS IN A CLINICAL SETTING

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Abstract: *Objective:* The study aims were to examine the relationship between adiposity and surrogate indices of pancreatic β -cell function and insulin sensitivity obtained from an oral glucose tolerance test (OGTT) in overweight adolescents and determine which factors best predict impaired glucose metabolism (IGM). *Methods:* In a sample of adolescents (n=209) severity of overweight was determined by relative body mass index (RBMI). Insulin sensitivity (QUICKI, CISI) and β -cell function (Fasting insulin: FI; Insulinogenic Index: $\Delta I_{30}/\Delta G_{30}$). *Results:* IGM was present in 26.8% (n=56), of which five had type 2 diabetes (T2DM). IGM prevalence was similar among RBMI strata. Once RBMI reached 150%, pronounced deterioration in CISI occurred (~55%) (P<0.0001) while less dramatic reductions were seen in QUICKI (P<0.05), with fasting blood glucose (FBG) and β -cell indices remaining stable. Compared to those with normal glucose tolerance, the IGM group exhibited higher β -cell activity (FI, P<0.0001; $\Delta I_{30}/\Delta G_{30}$, P=0.004) with reduced insulin sensitivity (CISI, P<0.0001; QUICKI, P<0.0002). CISI was the single predictor of IGM (P<0.0001). Low insulin sensitivity increased adolescents' chance for IGM (CISI: OR=6.49, 95%CI=2.63, 16.05, P<0.0001; QUICKI: OR=3.16, 95%CI=1.61, 6.05, P=0.0006) as did β -cell deterioration ($\Delta I_{30}/\Delta G_{30}$: OR=3.18, 95%CI=1.33, 7.59, P=0.0069). Normal FBG occurred in 37.5% of youth with IGM. *Conclusion:* The prevalence of IGM escalates in overweight adolescents, even at lower levels of overweight, and is associated with pronounced deterioration of insulin sensitivity. Current screening recommendations for FBG underestimate the prevalence of IGM in overweight adolescents thus limiting the opportunity for earlier intervention to prevent progression to diabetes.

Introduction

Obesity has reached epidemic proportions globally, affecting both children and adults (1). Childhood obesity has increased exponentially during the last 2 decades and the prevalence has tripled among adolescents, with both genders equally affected (2, 3). Overweight affects approximately 25% of European (4) and 30% of American children (5). Data from the National Health and Nutrition Examination Survey (NHANES) confirmed the increase in the prevalence of overweight in adolescents, with markedly greater increases in minorities (5). Childhood obesity tracks into adulthood (6, 7) and multiple studies link childhood obesity to subsequent morbidity and mortality in adulthood (8-12). Obesity markedly lessens life expectancy, especially among younger individuals. Severely obese (BMI > 45 kg/m²) young adults have a reduced life expectancy of 5–20 years (13). It has been suggested that, because of the health impact of obesity, this generation may be the first to live a shorter average lifespan than the preceding generation (14).

The progression of childhood obesity into adulthood is associated with early development of complications including Type 2 diabetes (T2DM). The pathogenic process involved in the deterioration of glucose metabolism starts during childhood (7, 15, 16). Delays in diagnosing and treating impaired glucose metabolism (IGM), enhance the chance of more severe cases and higher risk of complications in adulthood. Efforts to identify youth with IGM at incipient stages may justify early intervention and prevent the progression to T2DM along with

its known complications.

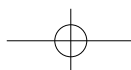
Deterioration in insulin sensitivity and the capacity of pancreatic β -cells to compensate for this decline in insulin sensitivity have been implicated in the development of T2DM. Insulin resistance syndromes and T2DM are increasingly common conditions diagnosed in children (17-22).

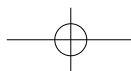
The interaction of factors such as increased adiposity, sedentary lifestyle, unhealthy eating habits, and hormonal changes associated with puberty, could exacerbate the insulin resistance state leading to IGM and diabetes, especially in genetically susceptible populations (15, 23-25). Assessment for T2DM is commonly triggered by the development of symptoms, rather than geared toward identification of children at risk who could benefit from early intervention. The lack of clinical indicators to identify those overweight/obese adolescents at higher risk of developing IGM precludes clinicians from early identification and more aggressive intervention to stop its progression to T2DM.

There is no definitive agreement about what screening tests best reflect the negative impact of increased adiposity on glucose metabolism in adolescents. The American Diabetes Association (ADA) and the Obesity Expert Committee recommend fasting blood glucose (FBG) as the preferred screening method and suggests adults and adolescents with impaired fasting glucose undergo an oral glucose tolerance test (OGTT) (17, 26, 27). However, there is an increasing body of evidence that fasting values of glucose clearly underestimated the risk and diagnosis of abnormal glucose metabolism in overweight and obese adolescents (28).

Received February 26, 2008

Accepted for publication March 3, 2008





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The OGTT was originally developed to classify carbohydrate tolerance (29), but it has become a widely used clinical tool to diagnose IGT/T2DM. The effectiveness and reliability of the OGTT to diagnosis IGT/T2DM in children have been previously demonstrated (28). Plasma glucose and insulin response during the OGTT reflect the ability of pancreatic β -cells to secrete insulin and the sensitivity of tissues to insulin. Consequently many investigators have studied and validated simple indices from glucose and insulin values obtained during the OGTT as surrogate measures of β -cell function and insulin resistance in children and adults (28, 30-39). In a biracial sample of adolescents, we have shown that the deterioration of insulin sensitivity as assessed by indices computed from OGTT are good clinical tools to identify those adolescents who are at higher risk for the development of IGM/T2DM (16, 40, 41). To expand our observations, we undertook the present study to examine the relationship between clinical measures of adiposity and surrogate indices of pancreatic β -cell secretory function and insulin sensitivity obtained from OGTT. A secondary focus was to determine which indicators of insulin sensitivity or β -cell function are the best clinical predictors of IGM in adolescents that are already overweight or obese.

Subjects and Methods

Two hundred and nine biracial overweight/obese children and adolescents participated in this investigation. The participants were recruited from individuals who were referred to the Lifestyle Clinic at LeBonheur Children Medical Center (Memphis, TN) for management of uncomplicated-obesity, or who participated in two NIH funded studies examining the impact of overweight on enteroinsular axis and markers of cardiovascular disease. To be included in the current study, participants were not taking any medications that affected glucose metabolism nor did they have any health-related conditions other than overweight or obesity. Study protocols were approved by the University of Tennessee Institutional Review Board. After signing an informed consent form, all individuals completed a physical examination and a 2-hour OGTT at the University of Tennessee General Clinical Research Center.

Measures of Adiposity

Body weight was obtained using a calibrated electronic scale with a precision of ± 0.02 kg. Height was measured to the nearest 0.1 cm using a calibrated stadiometer (Holtain Ltd, Crosswell, Crymych, United Kingdom). Body mass index (BMI) was calculated using the standard formula (weight in kg divided by height in meters squared) (17). The degree of excess weight, (relative BMI) was estimated using the BMI from the 50th percentile on the Center of Disease Control (CDC) BMI charts for age and gender. RBMI was calculated using the following equation: Participant's BMI/ BMI at 50th percentile for age and gender x 100. RBMI has been shown by our group to be a

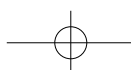
clinically useful tool to evaluate the severity and progression of overweight in children across ages, genders, and races plus it correlates with measures of body fat by dual energy x-ray absorptiometry (42). For analyses, the population was stratified into 5 RBMI categories ($125 \leq \text{RBMI} < 150\%$, $150 \leq \text{RBMI} < 175\%$, $175 \leq \text{RBMI} < 200\%$, $200 \leq \text{RBMI} < 250\%$, and $\geq 250\%$).

Laboratory Assays and Indices of Beta Cell Function and Insulin Sensitivity

After an overnight fast, a 2-hour OGTT was performed (29). Participants consumed 1 gm of dextrose per kg of body weight, up to 75 gm (Allegiance, MacGaw Park, IL), and blood samples were obtained at 0, 15, 30, 60, 90, and 120 minutes. The 2007 American Diabetes Association (27) diagnostic guidelines were used to categorize adolescents by glucose tolerance status based on OGTT values. Impaired glucose metabolism (IGM) was defined as a FBG ≥ 100 mg/dl or a 2-hour glucose level ≥ 140 mg/dl while subjects exhibited normal glucose tolerance (NGT) if FBG was < 100 mg/dl or a 2-hour glucose level during was < 140 mg/dl (27). Serum glucose was measured by the glucose oxidase method. Serum immunoreactive insulin levels were measured by standard double-antibody radioimmunoassay (RIA). Indices of β -cell insulin secretion and insulin sensitivity were computed using established formulas from both fasting and OGTT values of insulin and glucose. The β -cell insulin secretion capacity was assessed using the following indices: (a) fasting insulin (FI; expressed in $\mu\text{U/ml}$) and (b) Insulinogenic index ($\Delta I_{30}/\Delta G_{30}$) calculated as (insulin at 30 minutes - FI) / (glucose at 30 minutes - FBG) with insulin expressed in $\mu\text{U/ml}$ and glucose expressed as mg/dl (28, 36, 43, 44). Insulin sensitivity was assessed using (a) Composite Whole Body Insulin Sensitivity Index (CISI) calculated as $10000/(\text{SQRT}[(\text{FI} \times \text{FBG}) \times (\text{mean insulin of 0 through 120 minutes}) \times \text{mean glucose of 0 through 120 minutes}])$, and (b) Quantitative Insulin Sensitivity Check Index (QUICKI): $1/(\log \text{FI}_{\mu\text{U/ml}} + \log \text{FBG})$. Both CISI and QUICKI correlate with clamp measures of insulin sensitivity. (30, 32, 35, 38). QUICKI relies on fasting values, thus may reduce the burden (cost, family and staff time, and potential trauma to the child) associated with assessing insulin sensitivity.

Statistical Analyses

All data analyses were performed using the SAS system (Cary, NC). Descriptive statistics for continuous data are reported as mean and standard deviation of the mean (SD) for the entire sample and as mean and standard error (SE) for each group. Descriptive statistics for categorical data are reported as frequency and percent. Relationships between insulin indices, severity of overweight, and demographic characteristics were examined using Spearman Correlation Coefficients. Differences in insulin indices and demographic characteristics among RBMI groups and glucose status groups (IGM vs. NGT) were examined using Chi-square/Fisher exact test and



ASSESSING THE RISK OF IMPAIRED GLUCOSE METABOLISM IN OVERWEIGHT ADOLESCENTS

ANOVA/ANCOVA (controlling for RBMI) as appropriate. Logistic multivariate regression was used to predict IGM from indices and demographic variables. Odds ratios for IGM based on insulin indices, and the sensitivity/specificity of indices and FBG for IGM were calculated. P-values less than or equal to 0.05 were considered significant.

Results

Sample Characteristics

Two hundred and nine adolescents were included in the analysis. The characteristics for our study population were; age 14.6±1.92 y; weight 104.3± 26.6 kg; BMI 37.6 ± 7.6 kg/m²; RBMI 190.9 ± 36.6. Sixty-two percent were female and 65% African American (AA). Indicators of glucose metabolism for the study population were fasting blood glucose (FBG) 89.9±12.8 mg/dL; FI 31±27.2 μU/ml; $\Delta I_{30}/\Delta G_{30}$ 5.0±5.4; CISI 2.3±1.9; and QUICKI 0.3±0.3. No differences were found in age, weight, BMI, and RBMI between subjects with NGT and IGM (Table 1).

Table 1

Characteristics By Relative BMI Group and Glucose Tolerance Group

Relative BMI Group (n/%)	Age (yr)	BMI (kg/m ²)	RBMI	IGM (%)
125≤RBMI<150% (22/10.48)	14.5±0.4	27.8±0.8 ^b	141.7±4.0 ^b	13.6
150≤RBMI<175% (54/25)	14.6±0.3	31.9±0.5 ^b	163.3±1.1 ^b	35.2
≥175≤RBMI<200% (58/28)	14.4±0.3	36.3±0.5 ^b	186.5±1.1 ^b	24.1
200≤RBMI<250% (63/30)	14.7±0.2	43.2±0.5 ^b	219.4±1.7 ^b	29.0
RBMI≥250% (13/6)	14.3±0.5	53.2±1.0 ^b	275.5±6.8 ^b	15.4

Glucose Status Groups (n)	Age (yr)	BMI (kg/m ²)	RBMI	DM (%)
NGT (153)	14.5±0.2	37.6±0.3	191.6±3.1	0.00
IGM (56)	14.8±0.3	37.3±0.2	189.8±4.3	8.93 ^d

Values reported as mean±stderr. unless otherwise noted. a p<0.05 between RBMI group of ≥125<150% and other RBMI groups; b p<0.05 between RBMI groups with like symbol; d p<0.05 between glucose metabolism groups.

Insulin Sensitivity and Insulin Secretion Indices

RBMI Strata

Gender and race distribution was similar among RBMI strata. Mean age (Table 1) was similar among RBMI strata. FBG values and pancreatic β -cell indices (FI, $\Delta I_{30}/\Delta G_{30}$) did not provide a clear relationship with increasing RBMI (Table 2). However those in the highest RBMI group had higher $\Delta I_{30}/$

ΔG_{30} compared to the lowest RBMI group (P=0.04).

In contrast, indices of insulin sensitivity (QUICKI and CISI) demonstrated a persistent deterioration as the severity of overweight increased (P<0.01) (Table 2). CISI was reduced by 55% once RBMI increased above 150 (P<0.0001) and remained stable despite increased severity of overweight. QUICKI reflected a less drastic reduction in insulin sensitivity once RBMI increased over 150%.

Glucose Tolerance Status

Impaired glucose metabolism was present in 26.8 % (n=56) of the subjects (Table 1) of which five of these adolescents (8.9%) had no symptoms but meet the ADA criteria for diabetes. In twenty-one patients with IGM (37.5% of IGM), FBG was within normal range. The prevalence of IGM was similar among RBMI strata. There was a significant difference in FBG between NGT and IGT subjects, 86±1.0 vs. 99±1.7, P<0.0001, respectively. Indices of β -cell insulin secretion were higher (FI, and $\Delta I_{30}/\Delta G_{30}$) in the IGM group as compared to the NGT group (P <0.0001 and P=0.004 respectively) (Table 2).

Indices of insulin sensitivity were reduced in adolescents with IGM compared to NGT subjects, regardless of the severity of overweight (Table 2). When controlling for RBMI the differences in indices of insulin sensitivity remained significant between the NGT and IGT groups significant for both QUICKI (P = 0.0002) and CISI (P <0.0001) respectively.

For the entire cohort, we determined the risk for IGM based on established cut-points for CISI (45) and values selected based on scatter plots for QUICKI and $\Delta I_{30}/\Delta G_{30}$ (Figure 1) to identify insulin sensitivity cut-points at which impaired glucose intolerance occurred. Cut-points for the insulin sensitivity index were determined as: CISI ≤ 2.0 and QUICKI ≤ 0.30 and for $\Delta I_{30}/\Delta G_{30}$ ≤ 9.0 Using these cut-points, CISI identified 89.3% of youth with IGM while QUICKI and $\Delta I_{30}/\Delta G_{30}$ identified 78.6% of those with IGM.

Low insulin sensitivity, as assessed by CISI, increased adolescents' chance for IGM (CISI: OR=6.49, 95% CI= 2.63, 16.05, P<0.0001 and QUICKI: OR=3.16, 95% CI=1.61, 6.05, P=0.0006) as did β -cell deterioration ($\Delta I_{30}/\Delta G_{30}$: OR=3.18, 95% CI=1.33, 7.59, P=0.0069). Regardless of their overweight category, adolescents with IGM were six times more likely to have a CISI <2.0, and three time more likely to have a QUICKI ≤ 0.30 or a $\Delta I_{30}/\Delta G_{30}$ ≤ 9.0. Because 37.5% of youth with IGM had normal FBG, we compared the positive and negative predictive ability, sensitivity, and specificity of FBG, $\Delta I_{30}/\Delta G_{30}$, QUICKI, and CISI to identify those with IGM (Table 3). The negative predictive ability (true negative) of CISI was highest followed by FBG, $\Delta I_{30}/\Delta G_{30}$, and QUICKI. CISI was the most sensitive indicator of IGM while FBG had the highest specificity and positive predictive value.

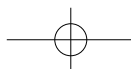
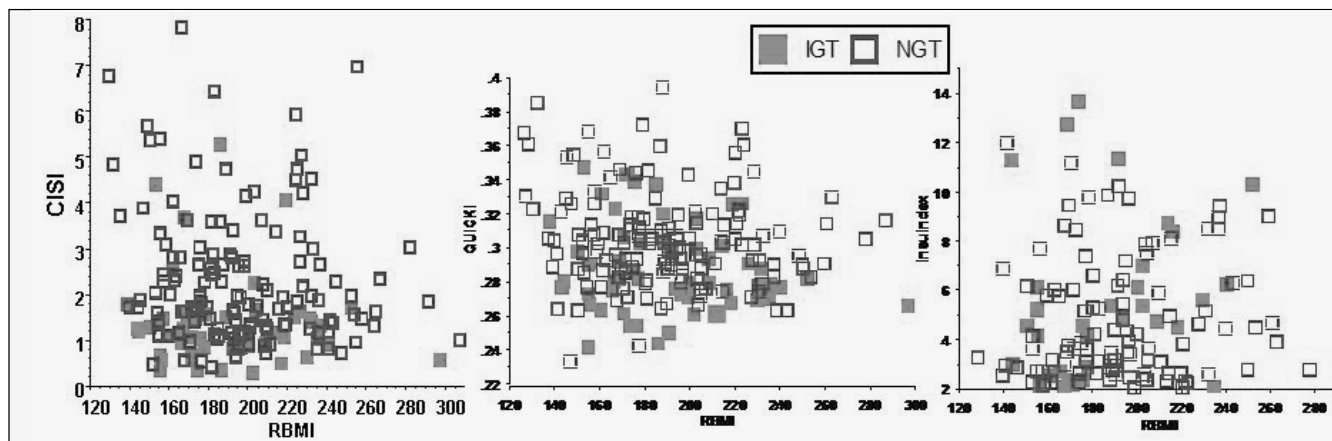


Table 2
Insulin Dynamic Indices Grouped by RBMI and Glucose Metabolism Groups

Relative BMI Group (n/%)	FBG (mg/dL)	Beta cell indices		Insulin Sensitivity Indices	
		FI (µU/ml)	$\Delta I_{30}/\Delta G_{30}$	CISI	QUICKI
125≤RBMI<150% (22/10.48)	85.6±3.0	26.2±5.8	2.5±1.3	4.7±0.4	0.33±0.01
150≤RBMI<175% (54/25)	91.1±1.9 ^c	33.2±3.7	5.2±0.7	2.1±0.2 ^a	0.30±0.01 ^a
≥175≤RBMI<200% (58/28)	88.9±1.8	32.6±3.6	5.3±0.7	2.2±0.2 ^a	0.30±0.01 ^a
200≤RBMI<250% (63/30)	91.4±1.8 ^b	32.4±3.5	5.0±0.7	1.9±0.2 ^a	0.31±0.01 ^a
RBMI≥250% (13/6)	81.8±3.9 ^{b,c}	29.2±7.6	6.7±1.5 ^a	2.9±0.5 ^a	0.31±0.01
Glucose Metabolism Group (n)					
NGT (153)	85.9±1.0	29.0±2.2	4.3±0.4	2.7±0.2	0.31±0.00
IGT (56)	99.0±1.7 ^d	39.8±3.6 ^d	6.9±0.7 ^d	1.4±0.3 ^d	0.29±0.00 ^d

Values reported as mean±stdev. For Glucose Metabolism Groups, adjusted mean ± stdev based on RBMI as a covariant. FBG: Fasting Blood Glucose; FI: Fasting Insulin; $\Delta I_{30}/\Delta G_{30}$: Insulinogenic Index; CISI: Composite Whole Body Insulin Sensitivity Index; QUICKI: Quantitative Insulin Sensitivity Check Index. a p<0.05 between RBMI group of ≥125<150% and other RBMI groups; b,c p<0.05 between RBMI groups with like symbol; d p<0.05 between glucose metabolism groups.

Figure 1
Distribution of insulin dynamic indices by glucose metabolism status in adolescents with obesity



Scatter plots for the entire cohort to establish cut-points values for CISI, QUICKI and Insulinogenic Index ($\Delta I_{30}/\Delta G_{30}$). Solid-squares ■ = IGT subjects, open-squares □ = NGT subjects. Cut-points for: CISI ≤2.0 and QUICKI ≤0.30 and for $\Delta I_{30}/\Delta G_{30}$ ≤9.0

Table 3
Fasting and OGTT Indices Ability to Predict Impaired Glucose Metabolism in Overweight/Obese Youth

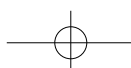
	Indices Derived from Fasting and OGTT Insulin and Glucose values			
	Fasting Blood Glucose	Insulinogenic Index	QUICKI	CISI
Sensitivity	0.6038	0.7586	0.7143	0.8929
Specificity	1.0000	0.0741	0.5556	0.4379
Positive Predictive Value	1.0000	0.2391	0.3704	0.3676
Negative Predictive Value	0.8844	0.500	0.7870	0.9178

Correlations between Severity of Overweight and Insulin Indices

The association between severity of overweight and indices of both β-cell insulin secretion and insulin sensitivity was examined. In the total cohort, only fasting insulin levels were significantly, but weakly, correlated with both BMI and RBMI (r= 0.15, P=0.03; r=0.16, P=0.02 respectively). We found a similar trend toward marginal correlations among the insulin sensitivity indices and both BMI (QUICKI: r= -0.12, P=0.09; CISI: r= -0.13, P=0.07) and RBMI (QUICKI: r= -0.12, P=0.07; CISI: r= -0.14, P=0.06).

Predictors of Impaired Glucose Tolerance

Univariate and multivariate analysis was performed to predict IGM as defined by FBG ≥100 mg/dl or a 2-hour glucose level ≥ 140 mg/dl. In our sample, IGM was not significantly



ASSESSING THE RISK OF IMPAIRED GLUCOSE METABOLISM IN OVERWEIGHT ADOLESCENTS

associated with age, gender, race, BMI, RBMI, or the $\Delta I_{30}/\Delta G_{30}$, but was associated with insulin sensitivity indices of QUICKI ($r = -0.23$, $P < 0.0001$) and CISI ($r = -0.32$, $P < 0.0001$). Multivariate logistic regression analysis revealed that low CISI was the single predictor of IGM in adolescents ($P < 0.0002$) followed by a trend of QUICKI to stay in the model ($P = 0.057$). Neither RBMI, BMI, age, gender or race accounted for the variance in CISI, QUICKI or $\Delta I_{30}/\Delta G_{30}$ values.

Discussion

Glucose homeostasis is maintained by the balance between insulin sensitivity and secretion (46, 47). In the clinical setting, simple methods of assessing the interaction between insulin sensitivity and secretion are important in the evaluation and follow-up of adolescents with obesity and risk factors for T2DM. Our results support the notion that at similar age, gender, and race distribution, adiposity affects glucose metabolism as suggested by the increased prevalence of subjects with IGM as the severity of overweight (RBMI) increases. However, in our sample of adolescents with wide-range of overweight, neither these differences in the prevalence of IGM reached significance among RBMI stratum nor did we find any difference in the BMI or RBMI between glucose tolerance groups (IGM vs. NGM) (Table 1). Correspondingly, we found no correlations between clinical markers of adiposity (BMI or RBMI) with glucose levels at fasting or 2 hr after glucose load and their correlations with FI and insulin secretion are weak.

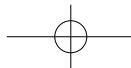
Our findings do not support the common practice of screening only kids with more severe overweight for IGM. Even in our lower RBMI category, the prevalence of IGM was ~ 3 times higher than expected in adolescents without overweight (48). Therefore, clinicians should consider individual factors other than severity of overweight when assessing adolescents for IGM, including: family predisposition, environmental factors (sedentary life style, dietary habits) race/ethnicity, underlying conditions, and treatments, hormonal and behavioral changes associated with puberty, etc.

Current screening guidelines favor FBG as the recommended method in subjects at risk for IGT or T2DM (17, 49). The results of this study are in agreement with other reports (28, 50), suggesting that a single FBG may not reflect the early impact of increasing adiposity on glucose homeostasis and could not discriminate between adolescents with and without abnormalities in the glucose metabolism until significant deterioration has occurred. In this study, IFG was one of the criteria to be included in the IGM category. Therefore, it is not surprising that the FBG was significantly different between the IGM and NGT groups. However, we have previously shown in a similar sample of adolescence that FBG is a poor predictor of IGT/T2DM and did not help to differentiate between subjects with IGT/DM or NGT (40, 45).

Similarly, Legro et al found that in women with polycystic ovarian syndrome, FBG would miss 58% of the diabetes diagnosis (51). The relatively low sensitivity and negative predictive values (0.60 and 0.88 respectively) of FBG observed in our sample denote its limitations for the screening of high-risk subjects. Based on these data, it can be estimated that approximately 37.5% of adolescents who have IGM will have a false negative FBG. Thus, the opportunity for earlier intervention to prevent progression in these patients will be missed (52).

Conversely, the OGTT provides clinically useful information that allows the estimation of insulin secretion capacity and insulin sensitivity, both of which are essential for defining the more affected pathway leading to IGM and helping clinicians to tailor treatment approach. These results agree with previous reports in that glucose levels 2 hours after glucose load have proved to be more successful in identifying earlier abnormalities in the glucose metabolism of adolescents (28, 53-55). Abnormality in post-prandial blood glucose typically preceded the deterioration in FBG (15, 28, 47). Impaired insulin sensitivity and secretion are the two main contributors to the pathogenesis of IGM/T2DM (56, 57). In children and adults, it has been shown that acute insulin response is the first measure to deteriorate, followed by second phase insulin secretion, and then fasting insulin (50, 56, 57). It also has been suggested that β -cell workload increases with overweight (58, 59). However, these results suggest that once the adolescents reach certain percentage of overweight or develop IGM, the relationship between β -cell function and adiposity is attenuated. Neither of the surrogate markers of β -cell secretory capacity (FI and $\Delta I_{30}/\Delta G_{30}$) documented a decline in insulin secretion ability. Contrarily, they suggested that in adolescents with IGM the insulin secretion capacity is maintained at a level that is at least equivalent to those with NGT. However, dysfunction in the insulin dynamics as shown in 1st and 2nd phases of insulin secretion, hepatic glucose production, glucagons secretion, and incretin hormone cannot be rule out from the results of this study. We agree with other investigators that the accuracy of surrogate estimates of β -cell function may diminish once IGM is present (39).

In agreement with other studies, our results demonstrate that deterioration of insulin sensitivity accompanying increasing overweight could be the most important pathogenic factor leading to impaired glucose metabolism among adolescents (50, 56, 57, 60). Insulin resistance is a multifactorial event that involves several molecular pathways in energy homeostasis, lipid metabolism, insulin receptor signaling pathway, cytokines, hormone-binding proteins including those that are serine protease inhibitors (SERPINS), and other protease regulators (22). Previously (40, 45), we found that obese adolescents, as compared with non-overweight adolescents, experienced a drastic reduction in insulin sensitivity as assessed by CISI. We found that there is a ~35% reduction on CISI values when comparing normal weight subject with those having lesser



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overweight ($125 \leq \text{RBMI} < 150$). Once the RBMI reaches 150% or higher, a maximum reduction of CISI (70%) has already occurred. Results of this study confirm that there is a marked deterioration in insulin sensitivity when comparing the least overweight adolescents with those who are heavier. This deterioration in insulin sensitivity reach a maximum once $\text{RBMI} \geq 150$. Impaired insulin sensitivity, as determined by lower CISI, was the best predictor of IGM in adolescents. In our prediction model, neither QUICKI, FI, nor $\Delta I_{30}/\Delta G_{30}$ were significant in predicting IGM in our sample. However, there was a trend for QUICKI to stay in the model ($P=0.06$). These results may be related to due to potential co linearity of QUICKI and CISI as both QUICKI and CISI incorporate fasting values of insulin and glucose. However, it may also reflect that the estimation of insulin sensitivity, based on fasting glucose and insulin concentrations, may also be influenced by the mixture of interrelated processes reflected in these values (i.e. hepatic glucose production, β -cell function, hepatic insulin extraction, insulin sensitivity). This interaction of processes may affect both the capacity to predict glucose intolerance as well as the sensitivity to detect earlier changes in insulin sensitivity in overweight adolescents.

Race, genetic predisposition, sedentary lifestyle, low socioeconomic status, duration of overweight, and underlying conditions are also major determinants of risk for IGM/T2DM in adolescents (61-63). However, not all adolescents with these characteristics develop IGM. The results of this study indicate that the use of surrogate markers to assess the interaction of insulin secretion and action may guide the clinician to identify individuals with higher risk for IGM and to implement a more intensive intervention. Several major reasons justify the need to identify and intervene in adolescents with overweight, who may be progressing to T2DM. These include: (1) Limited Federal Drug Administration (FDA)-approved drugs are available for the treatment of T2DM in children (64); (2) In youth, there is limited long-term information on safety and efficacy on drugs used for the treatment of T2DM; and (3) There are solid data supporting the benefit of weight loss, lifestyle interventions, and metformin in preventing/retarding progression to T2DM in subjects with IGT (15, 65, 66). Efforts to prevent the progression toward T2DM and further deterioration of β -cell function may delay the use of insulin and insulin secretagogues in obese adolescents, preventing the progression of weight gain induced by these agents.

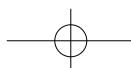
Because of the study design, our results may not be applicable to the general population; adolescents who were referred to our clinic and research programs tended to be severely overweight and may not be representative of the general adolescent population. Therefore, overestimation of the prevalence of abnormalities in glucose metabolism may be a consequence of a recruitment bias. Similar prevalence has been reported in other studies (67-69).

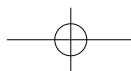
The potential effects confounding factors including family history, pubertal stage, physical activity or dietary habits were

not considered for this analysis. However, the independent impact of adiposity in glucose metabolism has been previously demonstrated in several studies even after correction for all these confounders (70, 71). We found no differences in age, gender, or race distribution among strata (severity of overweight or glucose status even after adjustment for severity of overweight). Our experience supports the notion that estimating the severity of overweight by RBMI could aid clinicians in assessing and comparing the magnitude and progression of overweight at different time-points of the growing period in an objective and practical way (41, 42). We have found that both BMI and RBMI were similarly associated with indices of glucose metabolism and insulin dynamics and cardiovascular risk factors in our population (40, 72-74). RBMI transforms BMI into a continuous variable relative to the ideal reference value (50th percentile on age and gender specific BMI charts) that reflects the severity of overweight, allowing a comparison across age and gender groups based on severity of overweight and facilitating longitudinal follow-up.

This study was not intended to validate any specific index to assess insulin dynamics. The use of surrogate markers of β -cell function and insulin sensitivity could imposes a limitation in the interpretation of our conclusions. Hyperglycemic, euglycemic-hyperinsulinemic clamp and frequently sampled intravenous glucose tolerance test (FSIVGTT) studies are the gold standard methods for assessing insulin sensitivity and β -cell function (75). However, these are not suitable for routine use in the clinical setting. In its place, we choose to use validated OGTT-derived indices of insulin dynamics. QUICKI has been extensively validated, and appears to have an excellent linear correlation with the glucose clamp and FSIVGTT index of insulin sensitivity (76, 77). In nonobese, obese, diabetic and hypertensive subjects, QUICKI showed a significant better linear correlation with the reference glucose clamp method than other surrogates including HOMA ($r = -0.66, P < 0.0001$; $r = 0.82, P < 0.0001$; $r = -0.68, P < 0.0001$; $r = 0.84, P < 0.001$ respectively) (75, 76). Likewise, Uwaifo et al (78) in a cohort of normal glucose-tolerant black and white children reported that FI, $\Delta I_{30}/\Delta G_{30}$ and QUICKI closely correlate with corresponding clamp-derived indices ($r = 0.86, P < 0.05$; $r = 0.70, P < 0.05$; $r = 0.69, P < 0.05$ respectively). Their results suggest that these indices have significant predictive value for estimating pancreatic β -cell secretion and insulin sensitivity in children. Hanson et al (79) has also reported the ability of FI and $\Delta I_{30}/\Delta G_{30}$ to predict the incidence of diabetes in Pima Indians and both indices demonstrated a significant correlation with AIRgluc ($r = 0.54$ and 0.58 respectively) in subjects with both impaired and normal glucose tolerance.

In regards to the CISI, it has also been shown to have a robust correlation with euglycemic clamp data in subjects with normal tolerance and IGT ($r = 0.73, P < 0.0001$; and $r = 0.66, P < 0.0001$, respectively), but these relationships are attenuated in individuals with T2DM ($r = 0.54, P < 0.00001$) (30). In a multiracial obese pediatric sample, Yeckel et al (55) using the





ASSESSING THE RISK OF IMPAIRED GLUCOSE METABOLISM IN OVERWEIGHT ADOLESCENTS

euglycemic-hyperinsulinemic clamp technique also reported that CISI has a greater correlation than HOMA with insulin-stimulated glucose metabolism (M value) ($r=0.78$, $r=0.57$ respectively).

In conclusion, the results of this study indicate that children with overweight are at increased risk for developing IGM. Clinicians taking care of these children should implement screening protocols in their practices that consider individual factors in addition to severity of overweight. Adolescents with overweight have a shorter latency to develop IGM and the interaction of individual factors (family history, race, pubertal stage, lifestyle and dietary habits, underlying condition and treatments) clearly impact insulin dynamics producing a pronounced deterioration in insulin sensitivity. Prospective, longitudinal studies examining glucose metabolism in overweight youth with normal glucose tolerance and impaired insulin sensitivity are needed to provide further validation of cut-points for impaired insulin sensitivity, as measured by CISI, in conjunction with lifestyle behaviors and family history, to predict IGM in overweight adolescents.

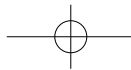
Fasting blood glucose may not reflect the early impact of increasing adiposity on glucose homeostasis and does not discriminate between adolescents with and without IGM until significant deterioration in glucose metabolism has occurred. Our findings provide support for revisions to the current practice guidelines of waiting until FBG values reach the impaired range before conducting an OGTT to assess glucose intolerance in overweight youth. Clinicians should be familiar and motivated to use OGTT-derived mathematical models to predict the risk for IGM and identify the more affected pathway.

Acknowledgments: This study was supported by funding from the National Center for Research Resources (NCR), (Grant Numbers RR0207887 and RR-00211) and the National Institute of Nursing Research (Grant Number NR008862) components of the National Institutes of Health (NIH), the Children's Foundation Research Center and the University of Tennessee General Clinical Research Center (UT-GCRC). Contents are solely the responsibility of the authors and do not necessarily represent the official views of NCR, NINR, NIH, or the Children's Foundation Research Center. The authors would like to thank Drs. Bruce Alpert, Dennis Black, and George Burghen for their guidance and support, the nurses at the Lifestyle Clinic and the UT-GCRC for their assistance in the care and evaluation of these subjects.

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