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I, Nancy Crimmins, hereby submit this original work as part of the requirements for the degree of:
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Prevalence and Predictors of Abnormalities in Carbohydrate Metabolism in a Cohort of Obese Youth

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Prevalence and Predictors of Abnormalities in Carbohydrate Metabolism in a Cohort of Obese Youth

A thesis submitted to the Graduate School of the University of Cincinnati in partial fulfillment of the requirements for the degree of Master of Science in the Department of Environmental Health of the College of Medicine by

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Abstract:

Abnormal glucose tolerance is becoming more commonplace in obese children and adolescents. We sought to determine the prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes (T2DM) in a cohort of 278 obese youth who had undergone oral glucose tolerance testing. We also sought to determine predictors of impaired glucose tolerance. The prevalence of IFG, IGT, and both IFG and IGT were 8.0%, 6.6%, and 1.8%, respectfully. Two individuals had 2-hour glucose concentrations which met diabetes criteria, and one individual had both fasting and 2-hour glucose concentrations which met diabetes criteria. Measures of insulin resistance (log HOMA-IR and log HOMA-β) were strongly associated with IGT. Non-Hispanic white race was found to be associated with isolated IGT and this relationship was strengthened when measures of insulin resistance were added to the model. We conclude abnormalities in glucose metabolism are common in obese youth, although overt diabetes is rare. Oral glucose tolerance testing should be considered in obese, insulin resistant non-Hispanic white youth with normal fasting glucose concentrations.
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Background:

Secondary to the obesity epidemic in children and adolescents, type 2 diabetes (T2DM) now accounts for approximately 30% of all diabetes cases in youth\(^1\). Despite this worrisome statistic, overall population estimates of the prevalence of type 2 diabetes is still low at 0.22 cases per 1000 youth\(^2\). However, recent population estimates of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are much more common in US adolescents at 13.1% and 3.4%, respectively\(^3\).

Little data exist regarding prevalence estimates of IFG, IGT and type 2 diabetes in cohorts of obese populations of youth—the group most at risk to develop disease. Previous reports have suggested that obese children and adolescents have rates of glucose intolerance and type 2 diabetes (T2DM) as high as 25% and 4% respectively\(^4\).

Type 2 diabetes can be “silent” yet can lead to cardiovascular complications if not detected and controlled. It is therefore critical to screen for glucose intolerance and T2DM in overweight and obese children and adolescents. The recommended screening tool for diabetes in obese youth is a fasting glucose\(^5-7\). However, the use of a fasting glucose only will miss those individuals with abnormalities of carbohydrate metabolism after glucose loads. Oral glucose tolerance testing will detect IGT but is costly and cumbersome. Identifying which obese children and adolescents based on history, anthropomorphic measures, and baseline laboratory assessment are most at risk for glucose intolerance and T2DM could lead to more judicious use of oral glucose tolerance testing.
We sought to determine the prevalence of IFG, IGT, and T2DM in a population of 278 obese black and non-Hispanic white children enrolled in a tertiary weight-loss program. In addition, we wanted to identify predictors of IGT with the goal of identifying individuals who might most benefit from oral glucose tolerance testing.

Methods:

Population: Healthworks! is a multi-disciplinary weight loss program for obese children and adolescents aged 5-20 years offered through Cincinnati Children’s Hospital Medical Center. The goal of the program is to promote a physically active lifestyle and healthy age-appropriate diet. Two hundred seventy eight overweight and obese (defined as the body mass index (BMI) ≥ 85th percentile) children and adolescents consecutively enrolled in the Healthworks! program (02/2003 through 07/2006) were included in this study. None of the participants were taking medication(s) known to affect carbohydrate metabolism and there were no pregnant females in the group.

Data Collection: All data was collected at the initial visit prior to any dietary or exercise intervention. Demographic data collected included age, sex, and race/ethnicity. Anthropomorphic data included height, weight, waist, and hip measurements. Waist measurements were done at both the level of the umbilicus and at the “natural” waist. Waist and hip measurements were done in duplicate and the average measurement was recorded. Height, waist and hip measurements were all obtained by one of four trained individuals for standardization. BMI was calculated as weight (kg)/ height (m)², and age- and sex-specific BMI percentiles and Z-scores were determined based on CDC growth charts⁸. Tanner staging was
assigned to each individual by a physician (if enrolled after 9/05) or by self-reporting using standardized photos for comparison (prior to 9/05). Tanner staging was recorded on 160/278 participants.

Oral glucose tolerance testing (OGTT) was performed following consumption of 1.75 g/kg (maximum 75 grams) Glucola by trained nursing staff in the Clinical Research Center of Cincinnati Children’s Hospital Medical Center. Participants were asked to fast for 10 hours prior to testing. Glucose and insulin concentrations were collected by venipuncture at before and 30, 60, and 120 minutes after glucose ingestion.

All data was entered in a password-protected database with limited access at the time of collection. Approval to conduct this study was obtained by the Institutional Review Board at Cincinnati Children’s Hospital.

*Laboratory:* Plasma samples were measured at the clinical laboratory at Cincinnati Children’s Hospital Medical Center. Glucose levels were determined using a glucose oxidase method and insulin concentrations were determined by radioimmunoassay.

*Definitions:* Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes was defined by ADA criteria\(^7\). Isolated IFG refers to individuals who had a normal fasting glucose but a 2-hour glucose concentration \(\geq 140\text{ mg/dL}\). HOMA-IR was defined as fasting insulin (mcU/mL) \(\times\) glucose (mmol/L) \(\div 22.5\) and HOMA-\(\beta\) was defined as \(20 \ast \) fasting insulin (mcU/mL) / [fasting glucose (mmol/L)-3.5]\(^6\). The insulinogenic index is calculated by the
ratio between insulin and glucose concentrations during the first 30 minutes post glucose load (ΔI₃₀:ΔG₃₀).

**Analysis:** All statistical analyses were conducted using the SAS system, version 9.1 (SAS Inc., Cary, NC). Prior to analyses, the data were examined for erroneous values and distributional properties. Two subjects were excluded from the study for obvious errors in data entry (a fasting insulin recorded as >500 mcU/mL and a fasting insulin of 1.5 mcU/mL, with an assay lower limit of 3 mcU/mL), leaving 278 subjects. Prevalence estimates for IFG, IGT, and T2DM were calculated for the overall group and by subsets of age: <10 years of age and ≥10 years of age. Two individuals did not have fasting blood sugars performed on oral glucose tolerance testing. Furthermore, one individual met criteria for diabetes by fasting glucose. Therefore, the denominator for the IFG prevalence calculation was 275 individuals. Because three individuals had a 2 hour glucose concentration ≥ 200 mg/dL, those individuals were not included in the prevalence calculation for IGT. Therefore, the denominator for IGT calculation was 275 individuals. To calculate the prevalence of having both IFG and IGT, the two individuals with no fasting glucose were removed as were the three that met diabetes criteria in some way. Thus the denominator for that calculation was 273 individuals.

Regression models using a backwards elimination approach were created with IGT as the dependent variable. BMI, BMI-Z, waist umbilicus, natural waist, waist umbilicus-to-hip ratio, natural waist-to-hip ratio HOMA-IR, HOMA-β, and insulinogenic index were independent variables of interest in the model. HOMA-IR and HOMA-β were log-normally distributed and therefore logHOMA-IR and logHOMA-β were used in the analysis. The contribution of each independent variable considered in the model was adjusted for age, sex, and race. Because
Tanner staging was available in only 57% of the individuals, and because of difference in collecting techniques, tanner staging was not included in the models. Because of the small numbers of individuals who were not either black or non-Hispanic white (n=6), the data from those individuals were not included in the models. Therefore, data from only 269 individuals were used in creating the models.

Results:

Demographic and anthropometric characteristics of the 278 participants are found Table 1. As a group, this population was quite obese with a mean BMI of 35.4 kg/m² and mean BMI-Z score of +2.5.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD (range) or percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.9 ± 3.1 (5.2-18.8)</td>
</tr>
<tr>
<td>Sex</td>
<td>63.6% female, 36.3% male</td>
</tr>
<tr>
<td>Race (White, Black, Other*)</td>
<td>52%, 46%, 2%</td>
</tr>
<tr>
<td>Pubertal Status (I, II-IV, V)</td>
<td>11%, 61%, 28%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.5 ± 7.6 [21.4-59.4]</td>
</tr>
<tr>
<td>BMI-Z score</td>
<td>2.5 ± 0.4 [1.5-4.2]</td>
</tr>
<tr>
<td>Waist Umbilicus (cm)</td>
<td>107.2 ± 2.0 [70.4-152.8]</td>
</tr>
<tr>
<td>Natural Waist (cm)</td>
<td>95.4 ± 14.7 [64.7-134.4]</td>
</tr>
</tbody>
</table>

*Other=Hispanic, Asian, and Multi-racial

Prevalence of IFG, IGT, and T2DM: The overall prevalence of IFG was 8.0% (22/275) and the prevalence of IGT was 6.55% (18/275). 1.8% of the study population had both IFG and IGT (5/273). Two individuals (0.7%) had normal fasting blood sugars but a 2 hour glucose concentration ≥200 mg/dL. One individual was diagnosed with T2DM with both a fasting
glucose concentration ≥126 mg/dL and a 2 hour glucose concentration ≥200 mg/dL. Thirty-eight subjects (38/278 or 13.7%) had some glucose abnormality.

Subjects greater than or equal to 10 years of age were more likely to have impaired fasting glucose (10.4% vs 2.7%, p=0.05) than subjects less than 10 years of age. However, even though the prevalence of IGT was almost double in those ≥10 years compared to those <10 years of age, this was not statistically significant (7.8% vs 4.1%, p=0.41) due to small numbers.

*Race and Sex Differences in the Prevalence of IGT:* It was decided a priori that models should be adjusted for age, gender and race, and the initial modeling involved only these variables. There were no sex differences in the prevalence of IFG or IGT. Although there were no statistically significant differences in the prevalence of IFG by race; however, there was a trend for subjects with IGT to be non-Hispanic white (p=0.06) when adjusted for age and sex. Furthermore, there were significantly more whites with isolated IGT (p=0.009) when adjusted for age and sex. There was no statistically significant race by sex interaction for either IFG or IGT.

*Predictors of IGT: Anthropomorphic Measures:* Neither BMI nor BMI-Z were significantly associated with IGT. Furthermore, neither natural waist, waist umbilicus, nor waist-to-hip ratios were significantly associated with IGT when adjusted for age, race, and sex.

*Predictors of IGT: Measures of Insulin Resistance and β-cell Function:* Both logHOMA-IR and log HOMA-β were strongly associated with IGT (p=0.0001 and p<0.0001, respectively) when adjusted for age, race, and sex. The insulinogenic index was not associated with IGT.
Predictors of IGT: Race and Measures of Insulin Resistance Combined Effect: The association of non-Hispanic white race with all IGT neared significance when adjusted for age and sex (p=0.06). When either log HOMA-IR or log HOMA-β were added to the model to account for insulin resistance, the effect of race then became statistically significant (p=0.04 for both).

Non-Hispanic white race was strongly associated with isolated IGT when adjusted for age and sex (p=0.009). When either log HOMA-IR or log HOMA-β were added to the model to account for insulin resistance, the effect of race became much stronger (p=0.005 for both).

Conclusion:
In this manuscript, we report prevalence data of abnormalities in carbohydrate abnormalities in a group of 278 obese children and adolescents. Diabetes was diagnosed in only one individual and only two additional individuals had 2-hour glucose concentrations over 200 mg/dL (with normal fasting glucose concentrations). Therefore, in our cohort of black and non-Hispanic white obese youth, undiagnosed diabetes was relatively uncommon despite a very high mean BMI.

IFG was more frequent in our cohort with a prevalence of 8.0%. Although not uncommon, this prevalence of IFG is actually less than what was reported from recent National Health and Nutrition Examination Survey (NHANES) data. Examining NHANES data from 2005-2006, Li et al reported the prevalence of IFG in 12-19 year old adolescents to be 13.1%\(^3\). Given that our subjects were all obese while the NHANES group was a population-based cohort including normal-weight adolescents, this is somewhat surprising. However, we had a younger cohort with
a mean age of 11.9 years. In addition, there were only six individuals in our group of Hispanic and Asian ethnicities and thus they were not included in our frequency estimates. These two differences might help to explain the discrepancies in findings.

The prevalence of IGT in our population was 6.5%. Sinha et al examined the prevalence of IGT in a multiethnic cohort of children and adolescents referred to a tertiary weight management clinic. The prevalence of IGT was found to be 25% in obese children (4-10 years of age) and 21% in obese adolescents (11-18 years of age). The reasons for the differences in IGT prevalence between our group and a similar group in terms of age and BMI are not completely clear. Again, our group did not include any individuals of Hispanic ethnicity whereas approximately 25% of the individuals studied by Sinha et al were of Hispanic ethnicity. Of interest, estimates of IGT have been similar to our findings (5-7.4%) in obese European populations 10-12.

As expected, measures of insulin resistance (HOMA-IR and HOMA-β) were directly associated with IGT and this finding was strengthened in subjects of non-Hispanic white race. Unexpectedly, the degree of obesity as measured by BMI, BMI-Z, waist or waist-to-hip ratios did not appear to increase risk of having IGT. Overall, our cohort was severely obese with a mean BMI of 35.5 kg/m2. We speculate that additional adiposity may not confer additional risk in those individuals already severely obese. These findings may be statistically driven as well: because all individuals had high BMI and waist values in our cohort, it may have been difficult to detect differences in IGT prevalence based on those risk factors.
Although black youth are thought to have slightly higher rates of type 2 diabetes than non-Hispanic whites\(^2\), we found that non-Hispanic whites were more likely than blacks to have isolated IGT. Furthermore, when adjusting for measures of insulin resistance (HOMA-IR and HOMA-\(\beta\)), this relationship was strengthened despite our relatively low numbers of subjects. These are the individuals who would not be determined to have prediabetes from a fasting glucose screen. Therefore, we speculate that obese white youth with normal fasting glucose might benefit from oral glucose tolerance testing, especially if a high-normal or abnormal glycated hemoglobin or strong family history of diabetes. Likewise, Li found that blacks had lower rates of prediabetes (either IFG or IGT) than non-Hispanic whites when studying the NHANES group\(^3\). We did not find a similar relationship between race and IFG.

One limitation of this study was the inability to use Tanner staging in our models given the inconsistency of obtaining and reporting Tanner staging. Because insulin sensitivity changes significantly during puberty, it would have been ideal incorporate Tanner staging in our models. As a less than ideal surrogate, we controlled for age in our models and age was not found to be associated with IGT. There was no difference in the frequency of IGT when comparing individuals who were less than 10 years of age (and unlikely to be mid-pubertal) to those above the age of 10. However there was a difference in the prevalence of IFG between the two groups with the older group having an increased frequency. Reasons why abnormalities in fasting glucose may be more age dependent than glucose two hours after a glucose load are not clear.

In summary, silent type 2 diabetes was relatively rare in our cohort of obese children and adolescents. IGT and IFG were more common than overt diabetes, although not as common as
previously reported in similar groups of children, and should be screened for when evaluating youth with obesity. Non-Hispanic white race and degree of insulin resistance was strongly associated with isolated IGT. As providers are likely to get an OGTT on anyone with IFG, oral glucose tolerance testing should also be considered in severely obese and insulin resistant non-Hispanic white youth with normal fasting glucose concentrations.
Bibliography: