**The Utility of Hemoglobin A1c in Detecting Prediabetes in Obese Youth**

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**Abstract:**

**Introduction.** The incidence and prevalence of Type 2 diabetes mellitus has been steadily increasing over the past ten years, and is currently approximately 4.1 per 1000 12-19 year olds in the US[2]. This increase has been linked to obesity and a sedentary lifestyle. Prediabetes, in the pediatric population is defined as having a fasting plasma glucose concentration ≥ 100 to 125 mg/dL or 2-hour glucose concentration during an oral glucose tolerance test ≥ 140 mg/dL but <200 mg/dL.

**Aims.** The goal of this study is to describe the sensitivity and specificity of hemoglobin A1c at various thresholds to identify prediabetes, as defined by impaired fasting glucose and/or impaired glucose tolerance; the population included in this study consist of obese youth referred to the Division of Endocrinology and Diabetes at Phoenix Children's Hospital for weight-related issues. We anticipate describing various levels of sensitivity and specificity of hemoglobin A1c in comparison with gold standard tests, such that it can be used to propel further studies to ultimately reduce the immense patient burden of fasting in the pediatric population.

**Methods**. We conducted a retrospective cross-sectional chart review and employed receiver operating characteristic (ROC) curve analysis of data including but not limited to hemoglobin A1c, fasting plasma glucose, and 2-hr post-prandial plasma glucose. The benefits of this study include the potential of reducing the patient burden of fasting prior to examination. This review will determine, if any, the potential value in being able to use hemoglobin A1c clinically to detect prediabetes in pediatric patients; determining this may provide critical information to improve the monitoring and screening of prediabetes.

**Conclusions**. Compared to the gold standards of fasting plasma glucose and oral glucose tolerance tests, we found that hemoglobin A1c had a low sensitivity and specificity for identifying prediabetes.

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**Introduction/Significance:**

Type 2 diabetes mellitus has become an increasing concern in pediatric patients in the US, accounting for thousands of type 2 diabetes diagnoses in children and adolescents every year, according to the SEARCH for Diabetes in Youth Study [1]. Until 1992, it was observed that only 3 to 10% of all new diabetes diagnoses in 10- to 19-year olds were type 2; by 1994, the percent of all new diabetes cases that were type 2 diabetes mellitus in this age group increased to 33% [2]. This increase has been linked to an increase in obesity and the presence of a sedentary lifestyle [3]. There is also a strong genetic component to type 2 diabetes, and this is displayed in the prevalence of particular racial groups; 45% of adolescents with diabetes were found to belong to minority populations [2, 3]. Specifically, 15-19 year old adolescent minorities diagnosed with diabetes, both type 1 and type 2, had a higher prevalence of having type 2 diabetes than type 1 [2].

The changes in glucose tolerance seen in those with Type 2 diabetes is the result of a decline in β-cell function secondary to insulin resistance; hyperglycemia can only occur if both conditions are present [3, 4]. Currently, the pathophysiology of type 2 diabetes can thus be explained through these two mechanisms. During the early years of prediabetes, normal or increased insulin levels are seen initially, but as the disease progresses, insulin secretion falls due to the decline in β-cell function, which allows for the onset of diabetes to take place [3, 5]. Normal β-cell response to peripheral glucose is dependent upon both β-cell mass and secretory capacity, and in the case of type 2 diabetes, the β-cells are unable to compensate adequately in the presence of insulin resistance [6, 7]. Insulin resistance induces changes in glucose homeostasis, by increasing demands on β-cells; β-cells then hypersecrete insulin in response to the insulin resistance, which is not sustainable for a long period of time, thus resulting in β-cell apoptosis [3, 6, 7] As the disease progresses, there is a marked decrease in beta cell secretory function, which in combination with insulin resistance results in hyperglycemia and thus type 2 diabetes [3, 5] The progression of insulin resistance to type 2 diabetes also appears to be linked to obesity, in addition to genetics, since increases in body weight have been associated with

decreased insulin sensitivity [5] In fact, during pre-diabetic years, an increased accumulation of lipids in the viscera, liver and muscles occurs intramyocellular accumulation of lipids has been discovered to be a key modulator of insulin sensitivity [5, 6, 8] Insulin resistance is correlated to the distribution of body fat, favoring higher levels of visceral fat over subcutaneous fat deposition; however, there are other environmental factors such as puberty, exercise, and diet that may complicate the assessment of insulin resistance [9, 10] .

Prediabetes, in particular, is defined as an intermediate stage of impaired glucose tolerance, between the progression from normal glucose tolerance to type 2 diabetes mellitus [8] . Proposed theories that explore the transition from impaired glucose tolerance to diabetes is that hyperglycemia may exacerbate the insulin resistance in addition to insulin secretory abnormalities [4] . Indications for screening for diabetes in pediatric patients include having a BMI > 85$^{th}$ percentile of for age and sex and two of the following characteristics: possessing a family history of type 2 diabetes in first and second degree relatives, belonging to a particular ethnic group (e.g. American Indians, Hispanic Americans, African Americans), and having signs of insulin resistance (acanthosis nigricans, hypertension, dyslipidemia); screening should occur every 2 years starting at age of ten [4] . The current gold standards of screening for diabetes include a fasting plasma glucose (FPG) test or a fasting 2-hour oral glucose tolerance test (OGTT) [11] . Prediabetes, by these standard tests, is defined as impaired fasting glucose (IFG) with an FPG of ≥100 to 125 mg/dL or impaired glucose tolerance (IGT) with a 2-hour glucose concentration during an oral glucose tolerance test of ≥ 140 mg/dL but <200 mg/dL [12] . Fasting plasma glucose is the preferred test, as it is more cost-effective, but the sensitivity and specificity of FPG has been shown to vary depending on the population in question; however, most studies declare that FPG is clinically acceptable in terms of its sensitivity and specificity [4] . The OGTT is also known as a gold-standard test to screen for diabetes, with a specificity of approximately 95% and a sensitivity of 50% in the adult population [13] .

However, both tests require patients to fast prior to the test; this poses a particularly significant barrier to screening in the pediatric population [14] . Glycated hemoglobin or hemoglobin A1c (HbA1c) is currently used to monitor the progression of diabetes in adults; the benefits of HbA1c use as a screening tool over the current gold standards exists in its

convenience, where fasting is not required, and in its prediction of diabetes complications [15-17] . Although the American Diabetes Association (ADA) has recently included HbA1c in its diagnostic criteria in adults with diabetes (HbA1c ≥6.5%) and prediabetes (HbA1c 5.7 to <6.5%), HbA1c has not been well-studied as a screening method in pediatrics and recommendations in children are based on limited data [4, 15, 16] . The goal of this study is to describe the sensitivity and specificity of HbA1c at various thresholds to identify prediabetes in the pediatric population and to discuss the implications of these values.

**Research Materials and Methods:**

The patients eligible for this study were pediatric patients referred to the Division of Endocrinology and Diabetes at Phoenix Children's Hospital (PCH) for evaluation of weight-related health conditions, such as hyperglycemia, dyslipidemia, and hypertension. These 450 patients were seen from April 2010 to February 2012 and were included in the study if they had a hemoglobin A1c level as part of their work-up. Patients excluded from the study were patients not referred to PCH for weight-related issues and patients who did not have fasting plasma glucose tests, oral glucose tolerance tests, and hemoglobin A1c levels as part of their work-up. As this study involved data with human subjects, IRB approval was obtained; patients were identified by multiple mechanisms, including ICD-9 codes, billing codes, and daily clinic schedules.

Categories of dysglycemia were identified based on the American Diabetes Association definitions: prediabetes was defined by patients having an FPG level of 100-125mg/dL (impaired fasting glucose or IFG) or OGTT level of 140-199 mg/dL (impaired glucose tolerance or IGT), hemoglobin A1C values between 5.7 and 6.4 percent or a combination of these factors. Type 2 Diabetes was defined by patients having an FPG level > 126 mg/dL, OGTT > 200mg/dL, or hemoglobin A1c >6.5. Data was collected from the medical record, de-identified, and analyzed using SPSS (Software Package for Social Scientists). Frequencies were used to describe the demographic and glycemic characteristics of the study population. Receiver operating characteristic (ROC) curve analysis was used to generate the sensitivities (the percentage of patients with type 2 diabetes diagnosed based on American Diabetes Association (ADA) guidelines of fasting plasma glucose or 2-hr plasma glucose) and specificities (the percentage of patients who do not have type 2 diabetes who have been correctly excluded from the diagnosis based on ADA guidelines of fasting plasma glucose and 2-hr plasma glucose) of hemoglobin A1c in comparison to the gold standards.

## Results:

### Characteristics of the study population

The population of 450 pediatric patients that were included in the study consisted of patients between the ages of three years and nineteen years of age, with a mean age of 12.41 ± 3.09. 54.7% of the patients in the study were female, while 45.3% were male. 51.6% of the population were Hispanic, 6% were African American, 21.2% were Caucasian, 2.2% were Asian, 5.1% were Native American, and 13.5% other or missing (Table 1). About three quarters of the population had acanthosis nigricans, a characteristic associated with insulin resistance, upon presentation, while 20% did not present with acanthosis nigricans (Table 2). As the patients included in this study were included due to referrals for weight-related health issues, the mean BMI for the patients in the study was 32.99, with the maximum BMI of 59.7.

### Glycemic status of study population

The average hemoglobin A1c of the cohort was 5.7 ± .286 which is also the lower end of the threshold of diagnosing prediabetes using only hemoglobin A1c. The percentage of patients with normal glycemic status by fasting plasma glucose and 2-hour oral glucose tolerance test was 85.6% and 88%, respectively (Table 3). 10.4% of the patients were found to have prediabetes defined by impaired fasting glucose and 8.3% of the patients were found to have prediabetes defined by impaired glucose tolerance. 52.2% of the 450 patients included in the study had normal hemoglobin A1c, while 47.8% of patients had a hemoglobin A1c within range of prediabetes. However, none of the patients had a hemoglobin A1c within range of Type 2 Diabetes. 79.3% of patients had normal glycemic status defined by fasting plasma glucose, oral glucose tolerance test, and hemoglobin A1c, whereas 16% had values falling into the prediabetic or diabetic range defined by the same three criteria.

### Sensitivity and specificity analysis of hemoglobin A1c for diagnosing prediabetes compared to gold standards

The median sensitivity and specificity of hemoglobin A1c when compared to fasting plasma glucose is 59.6% and 60.4%, respectively (Table 4). The maximum sensitivity of hemoglobin A1c when compared to those diagnosed with impaired fasting glucose was 95.7%, which corresponded to a specificity of 15.6%; the maximum specificity for this same data set was 99.7%, which corresponded to a sensitivity of 2.1%. The median sensitivity and specificity of hemoglobin A1c when compared to oral glucose tolerance tests is 45.75% and 59%, respectively. The maximum sensitivity of hemoglobin A1c when compared to those diagnosed with impaired glucose tolerance was 94.3%, which corresponded to a specificity of 0.8%; the maximum specificity for this same data set was 99.0%, which corresponded to a sensitivity of 2.9%. The median sensitivity and specificity of hemoglobin A1c when compared to both fasting plasma glucose and oral glucose tolerance tests is 50.7% and 60.35%, respectively. The maximum sensitivity of hemoglobin A1c when compared to those diagnosed with impaired fasting glucose or impaired glucose tolerance or both was 97.2%, which corresponded to a specificity of 0.8%; the maximum specificity for this same data set was 99.7%, which corresponded to a sensitivity of 1.4%.

Table 1. Demographic Characteristics of the Patient Population

| Variables | Mean (SD) |
|---|---|
| Age (years) | 12.41 (3.09) |
| Gender | |
| Male | 45.3 |
| Female | 54.7 |
| Ethnicity | 21.1 |
| Caucasian | 6.0 |
| African American | 51.6 |
| Hispanic | 2.2 |
| Native American | 5.1 |
| Other | 7.3 |
| Missing Data | 6.7 |

Table 2. Clinical Characteristics of the Patient Population

| Variables | |
|---|---|
| | Mean (SD) |
| BMI | 32.9 (6.8) |
| Glucose Fasting | 90.7 (7.1) |
| Glucose 2 hours | 106.7 (23.9) |
| TSH | 174.1 (375.3) |
| HbA1c | 5.7 (0.286) |
| Insulin Fasting | 30.5 (23.0) |
| Insulin 2 hours | 110.9 (116.6) |
| LDL-C | 174.5 (262.6) |
| HDL-C | 44.6 (9.1) |
| Triglyceride | 132.3 (78.9) |
| Total Cholesterol | 165.9 (82.8) |
| | % |
| Acanthosis | |
| Present | 75.1 |
| Absence | 20.0 |
| Missing data | 4.9 |
| Tanner Stage | |
| Stage 1 | 26.4 |
| Stage 2 | 8.4 |
| Stage 3 | 6.7 |
| Stage 4 | 4.7 |
| Stage 5 | 4.9 |
| Missing Data | 48.9 |

Table 3. Frequency of dysglycemia measured by any increase in FPG, OGTT, HbA1c, or all categories

| Variable | Sub-Category | % |
|---|---|---|
| FPG | | |
| | NPG1 | 85.6 |
| | Pre-Diabetes | 10.4 |
| | Type 2 Diabetes | 0.0 |
| | Missing Data | 4.0 |
| OGTT | | |
| | NGT2 | 88.0 |
| | Pre-Diabetes | 7.3 |
| | Type 2 Diabetes | 0.4 |
| | Missing Data | 4.3 |
| HbA1c | | |
| | Normal (<5.7%) | 52.2 |
| | Prediabetes (5.7 - 6.4%) | 47.8 |
| | Missing data | 0 |
| All Categories | | |
| | NPG, NGT, HbA1c < 5.7% | 79.3 |
| | Any elevation of FPG, OGTT, or HbA1c | 16.0 |
| | Missing data | 4.7 |

1 Normal fasting glucose (NFG): glucose < 100 mg/dL; Prediabetes: glucose 100-125 mg/dL; Type 2 Diabetes: glucose > 125 mg/dL

2 Normal glucose tolerance (NGT): glucose < 140 mg/dL; Prediabetes: glucose 140-199 mg/dL; Type 2 Diabetes: glucose > 200 mg/dL

Table 4. Sensitivity and Specificity of HbA1c compared to FPG, OGTT, and FPG & OGTT respectively.

| HbA1c by FPG | | HbA1c by OGTT | | HbA1c by FGP and OGTT | |
|---|---|---|---|---|---|
| Sensitivity | Specificity | Sensitivity | Specificity | Sensitivity | Specificity |
| 100.0% | 0.0% | 100.0% | 0.0% | 100.0% | 0.0% |
| 100.0% | 0.3% | 100.0% | 0.3% | 100.0% | 0.3% |
| 100.0% | 1.3% | 94.3% | 0.8% | 97.2% | 0.8% |
| 100.0% | 4.7% | 94.3% | 4.3% | 97.2% | 4.5% |
| 100.0% | 7.8% | 91.4% | 7.1% | 94.4% | 7.3% |
| 95.7% | 15.6% | 82.9% | 14.6% | 88.9% | 15.4% |
| 89.4% | 25.2% | 80.0% | 24.2% | 83.3% | 25.2% |
| 87.2% | 39.7% | 68.6% | 37.6% | 76.4% | 39.8% |
| 66.0% | 54.0% | 48.6% | 52.3% | 55.6% | 53.8% |
| 53.2% | 66.8% | 42.9% | 65.7% | 45.8% | 66.9% |
| 38.3% | 77.1% | 37.1% | 76.5% | 36.1% | 77.6% |
| 29.8% | 87.3% | 28.6% | 86.6% | 27.8% | 88.0% |
| 14.9% | 93.0% | 11.4% | 92.4% | 12.5% | 93.0% |
| 14.9% | 95.8% | 8.6% | 94.9% | 11.1% | 95.8% |
| 4.3% | 97.9% | 5.7% | 98.0% | 4.2% | 98.0% |
| 4.3% | 99.2% | 2.9% | 99.0% | 2.8% | 99.2% |
| 2.1% | 99.7% | 0.0% | 99.5% | 1.4% | 99.7% |
| 0.0% | 100.0% | 0.0% | 100.0% | 0.0% | 100.0% |

*Values derived from ROC curve

**Discussion:**

In conducting our study in a population of children referred to a tertiary care center for weight-related issues, we found that hemoglobin A1c had a low sensitivity and specificity for identifying prediabetes compared to the gold standards of fasting plasma glucose and oral glucose tolerance tests. 47.8% of patients had a hemoglobin A1c within criteria for prediabetes; however, when compared to the fasting plasma glucose and the oral glucose tolerance tests, 10.4% and 7.3% of patients met criteria for prediabetes. This indicates that hemoglobin A1c may be over-predicting prediabetes within this population when using the cutoffs established in the adult population. There have been few studies in the pediatric population that examine cutoffs for the sensitivity and specificity of hemoglobin A1c; however, it was shown in previous studies that A1c alone is not an accurate diagnostic measure of type 2 diabetes in obese children and adolescents[17]. This may also be true of hemoglobin A1c in regards to classifying prediabetes, and the data extrapolated from our study does imply a lower sensitivity and specificity compared to not only the gold standards, but also compared to hemoglobin A1c reported in adults.

In viewing data presented by the National Health and Nutrition Examination Survey, an A1C level of 5.8% showed the highest sensitivity of 86% and specificity of 92% in identifying undiagnosed diabetes when using FPG as the diagnostic test for type 2 diabetes[18]. This is markedly higher than any of the values derived from the ROC curves at all cutoffs of hemoglobin A1c that are shown in Table 4. Furthermore, fasting plasma glucose, as mentioned before, has been reported in adults to have a sensitivity and specificity that vary depending on the population in question but is determined to be clinically useful. The OGTT is known to have a specificity of 95% and a sensitivity of 50% in the adult population, which again, is higher than the values of sensitivity and specificity derived from our data for this population. This implies that there may be benefit to not ordering a hemoglobin A1c in the workup of these children or only ordering a hemoglobin A1c after initial screening with FPG or OGTT, as this may not have the diagnostic capability of the current gold standards. This could also act in a manner to conserve healthcare costs; in one study, it was found that there was a high cost per case of

screening for Type 2 diabetes in adolescents, with costs ranging from $312 000 to $831 000 per case identified[19]. The cost of an individual hemoglobin A1c test was cited to be $13.90 per screen; though this number is small, lowering unnecessary laboratory testing would prove to be fruitful in saving healthcare costs. Further studies are needed in order to truly make these conclusions.

Limitations within this study are further discussed: this study had a population where up to 10% of the included individuals had dysglycemia by the gold standards of fasting plasma glucose and oral glucose tolerance tests or both. Because the population studied had a smaller number of those with the characteristic of interest, there is less power in this study and the data may not be generalizable. In addition, the population included was a small subset of patients referred to a tertiary care center, which does not represent a large portion of the population that is seen at primary care centers. There were also missing data points from the database, which is due to the fact that not all patients had the same lab tests during their work-ups; having complete data sets would have increased the power of the study. Furthermore, there was not a large enough sample size to draw accurate optimal thresholds for hemoglobin A1c that would maximize the sensitivity and specificity; having the ability to optimize a cutoff that would maximize these values may indicate that a new cutoff should be used for the pediatric population.

**Future Directions:**

Future studies should include a larger population with a larger percentage of individuals with dysglycemia, as only 7-10% of those included in this study had dysglycemia based on the gold standards. In addition, a prospective study may mitigate the issue of missing data; this was a sub-optimal condition for this study, and conducting a prospective study would potentially control for data missing, which is the disadvantage of a retrospective study. Prospective studies could also investigate the utility of hemoglobin A1c in the long-term outcomes of pediatric patients with prediabetes or type 2 diabetes.

**Conclusions:**

Compared to the gold standards of fasting plasma glucose and oral glucose tolerance tests, we found that hemoglobin A1c had a low sensitivity and specificity for identifying prediabetes in a population of children referred to a tertiary care center for weight-related issues. Further prospective investigation into the role of hemoglobin A1c as a screening tool should be undertaken, as it could be beneficial to establish new cutoffs in the pediatric population that maximizes the sensitivity and specificity in identifying prediabetes and diabetes. In addition, there could potentially be a benefit to not perform the test, as it could serve to save healthcare costs, if it is determined to be a test with low sensitivity and specificity in larger populations.

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