

## Abstract

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<sup>2</sup>. 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. 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. 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.

## Introduction

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<sup>1</sup>. 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<sup>3</sup>. 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)<sup>11</sup>. Prediabetes, by these standard tests, is defined as impaired fasting glucose (IFG) with an FPG of  $\geq 100$  to 125 mg/dL or impaired glucose tolerance (IGT) with a 2-hour glucose concentration during an oral glucose tolerance test of  $\geq 140$  mg/dL but  $< 200$  mg/dL<sup>12</sup>. Both tests require patients to fast prior to the test posing a barrier to screening in the pediatric population<sup>14</sup>. 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<sup>15-17</sup>. 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.

## Methods

The 450 patients included in this study were pediatric patients referred to the Division of Endocrinology and Diabetes at Phoenix Children's Hospital (PCH) for weight-related health conditions, such as hyperglycemia, dyslipidemia, and hypertension between April 2010 to February 2012 and were included in the study if they had a hemoglobin A1c level as part of their work-up. Dysglycemia was defined by American Diabetes Association definitions. 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 and specificities of hemoglobin A1c in comparison to the gold standards.

## Results

**Patient population characteristics.** Patients included in the study were between ages of three and nineteen years, with a mean age of  $12.41 \pm 3.09$ . 54.7% of the patients in the study were female, while 45.3% were male (Table 1). As the patients included in this study were referred for weight-related health issues, the mean BMI for the patients in the study was 32.99, with the maximum BMI of 59.7.

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 1. Demographic Characteristics of the Patient Population

**Glycemic Status of Patient Population.** The average hemoglobin A1c of the cohort was  $5.7 \pm .286$ . 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 IFG and 8.3% of the patients were found to have prediabetes defined by IGT. 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. 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.

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

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

**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 median sensitivity and specificity of hemoglobin A1c when compared to oral glucose tolerance tests is 45.75% and 59%, respectively.

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.

HbA1c by FPG		HbA1c by OGTT		HbA1c by FPG 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%
4.3%	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

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

## Discussion and Conclusions

We found that hemoglobin A1c had a low sensitivity and specificity for identifying prediabetes compared to the gold standards of FPG and OGTT. 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. This implies that there may be benefit to not ordering a hemoglobin A1c in the workup of these. 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<sup>19</sup>. 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.

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