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Hemoglobin A1C and the Diagnosis of Diabetes and Prediabetes in Children and Adolescents

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Hemoglobin A1C and the Diagnosis of Diabetes and Prediabetes in Children and Adolescents

A Dissertation
Presented for
The Graduate Studies Council
The University of Tennessee
Health Science Center

In Partial Fulfillment
Of the Requirements for the Degree
Doctor of Philosophy
From The University of Tennessee

By
Jennifer McGuire Hitt
December 2014

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DEDICATION

This dissertation is dedicated to my daughter,
Mary Carter Hitt.
My world begins and ends with you.

ACKNOWLEDGEMENTS

I would like to thank my committee, Dr. Donna Hathaway, Dr. Mona Wicks, Dr. Margaret Hartig, and Dr. Matt Strum. Your advice and encouragement were invaluable. In addition, my thanks and sincerest gratitude to my committee chair, Dr. Patricia Cowan, who served not only as a chair, but as a treasured mentor.

ABSTRACT

Although the American Diabetes Association (ADA) adopted the use of the glycosylated hemoglobin (A1C) test as a method of diabetes and prediabetes diagnosis, the ADA has not developed firm guidelines concerning the use of the A1C test in children and adolescents, as research has not validated thresholds in this group. Diabetes and prediabetes are diseases influenced by multiple factors, including race and ethnicity, age, vitamin D deficiency, and body mass index (BMI).

The purpose of this study was to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the A1C test compared to the gold standard use of the fasting plasma glucose (FPG) and 2-hour oral glucose tolerance test (OGTT) to detect diabetes and prediabetes in a children and adolescents considered to be at higher risk for impaired glucose metabolism. In addition, ROC curve analysis was performed to determine optimal thresholds for the diagnosis of prediabetes in available groups of the research sample. The study also examined the correlation between A1C and race and ethnicity, age, vitamin D levels, and body mass index, in addition to comparing the relationship of A1C to beta cell dysfunction and insulin sensitivity.

A retrospective review of 902 patient electronic medical records in an urban endocrinology clinic was conducted. Based on FPG and 2-hr glucose during the OGTT, patients were classified based on the ADA 2014 criteria as having diabetes or prediabetes. Subjects ranged in age from 2-18 (11.6 ± 3.32), were predominantly minority (70.7% African American, 17.3% Hispanic, 12.0% Caucasian) and female (60.7%). The results yielded a high specificity (99.7%) and high negative predictive value (99.9%) for the whole sample, although the results were lower for the African American group. The results also yielded a low specificity (35.3%) but a high negative predictive value (99.8%) for the entire sample. Although results were once again lower for the African American subset. ROC curve analysis for prediabetes yielded a threshold of 5.8% for sample. Multiple regression found some correlation between fasting glucose and A1C, although statistical analysis was not possible for the aggregate sample. No statistically significant association was found between the A1C and age, vitamin D, and BMI in the sample. Correlation analysis found stronger associations between the A1C and beta cell dysfunction versus insulin sensitivity.

In this predominantly minority population A1C had a high specificity and sensitivity for the diagnosis of diabetes. While the A1C resulted in a high number of false positives for prediabetes, A1C $<5.7\%$ accurately identified individuals with normal glucose tolerance. Children and adolescents considered to be at higher risk for impaired glucose metabolism (family history of diabetes, obesity, minorities, or history of gestational diabetes) with A1C $\geq 5.7\%$ or with symptoms of diabetes should undergo OGTT testing. In addition, different threshold levels for racial and ethnic groups should be considered in the diagnosis of prediabetes.

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LIST OF ABBREVIATIONS

β -cell	Beta cell
ADA	American Diabetes Association
ANOVA	Analysis of Variance
AUC	Area under curve
BMI	Body mass index
CDC	Center for Disease Control
CIR30	Corrected insulin response
CISI	Composite index of insulin sensitivity
HOMA	Homeostasis model assessment
IDF	International Diabetes Federation
IECR	International Expert Committee Report
IGI	Insulinogenic index
INS0	Fasting insulin
FPG	Fasting plasma glucose
NHANES	National Health and Nutrition Examination Survey
NPV	Negative predictive value
OGTT	Oral glucose tolerance test
PPV	Positive predictive value
QUICKI	Quantitative insulin sensitivity check index
ROC	Receiver operator curve
SAS	Statistical Analysis Software
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

CHAPTER 1. INTRODUCTION

Background

Diabetes is a growing epidemic among children and adolescents in the United States. A recent report from the Centers for Disease Control (CDC) noted that 23% of children in this country suffer from diabetes or prediabetes, which is an increase from 9% one decade earlier (CDC, 2012). The majority of the increase is directly linked to the increase in obesity, high fat diets, sedentary lifestyles among child and adolescents (May, Kuklina, & Yoon, 2012). With the prevalence of diabetes and prediabetes growing, cost-efficient and timely methods are needed to identify children and adolescents with the disease. Most criteria for the diagnosis of diabetes and prediabetes are based on adult values. To date, there have been no systematic studies validating the appropriateness of glycated hemoglobin A1C (A1C) for use in children. With the increased need to identify youth with this disease, the methods for diagnosis diabetes and prediabetes in younger groups should be further refined.

The most common method to diagnose diabetes has been the oral glucose tolerance test. More recently, the use of the (A1C) tests has been supported by several organizations. However, the use of A1C testing to identify individuals at-risk for the development of diabetes has been controversial (ADA, 2007; McCarter, Hempe, Gomez, & Chalew, 2004). The International Expert Committee, appointed by the American Diabetes Association and European Association for the Study of Diabetes, concluded in 2009 that A1C testing can effectively identify individuals at lower risk for developing diabetes (ADA, 2014). However, the committee did warn of limitations regarding the use of the test, including inconsistencies in correlating the A1C test to that of the fasting glucose results, the overall cost, and availability of the test. Moreover, the committee found that the A1C tests do not accurately or precisely diagnose diabetes compared to other tests, such as oral glucose tolerance testing or average glucose concentrations (McCarter, Hempe, Gomez, & Chalew, 2004).

The strength of A1C testing is that it most closely correlate with mean glucose concentrations over time, compared to the oral glucose tolerance test that correlates more closely with post prandial glucose concentrations (Nathan, Turgeon, & Regan, 2007; Rohlfing, et al., 2002) . In addition, A1C testing has been shown to be effective in predicting development of diabetes mellitus associated complications, such as the likelihood of developing diabetic retinopathy and nephropathy (Wang, et al., 2011). The test has also been most closely linked to morbidity and mortality rates among persons with diabetes mellitus (Boltri, Okosun, Davis-Smith, & Vogel, 2005). However, there have been mixed results showing the use of A1C with disease prediction methods. Most research suggests prediction of diabetes mellitus is best done with challenged oral glucose testing in addition to A1C testing (Stern, Williams, & Haffner, 2002; Peter, et al., 2007). As the cost of health care continues to rise, finding economically feasible prediction methods should be examined.

Little research exists with regard to the use of A1C testing in children or adolescents. The International Committee (2009) recommended the A1C test be used in symptomatic adolescents. However, limited research exists with its use in children (Lee, En-Ling, Tarini, Herman, & Yoon, 2011; Nowicka, et al., 2011). In addition, thresholds for the use of the A1C tests were established in adults. Appropriate thresholds have not been thoroughly researched in children or adolescents (Nowicka, et al., 2011).

With regard to the accuracy of A1C testing, research has indicated several covariates influence A1C. Racial and ethnic groups show statistically significant differences in the correlation of A1C to mean serum glucose concentrations (Herman, et al., 2007; Herman et al., 2009; Kirk, et al., 2008). Studies have shown variations in A1C among different racial groups, whereas mean plasma glucose concentrations do not vary between racial groups. These preliminary results suggest a biological basis for the variability across racial groups with respect to A1C testing (Bonds, et al., 2003; Christensen, et al., 2010; Cohen, 2007). Vitamin D levels also have been correlated inversely to A1C, although the direct link between Vitamin D and diabetes has yet to be firmly established (Kositsawat, Freeman, Gerber, & Geraci, 2010). In addition, some research suggests A1C differ based on beta cell function and insulin resistance (Kim, et al., 2012). Research is needed to more clearly identify how these factors influence A1C, especially in children, so that appropriate guidelines can be established for the use of A1C test as a diagnostic test.

Significance

The current study was conducted to build on prior research exploring A1C and covariate factors. However, this study examined individuals at earlier ages. Most noted research on this topic used participants with mean ages ranging from 50-60 years (Boltri, Okosun, Davis-Smith, & Vogel, 2005; Christensen, et al., 2010; Kirk, 2008). Based on a review of data available, the mean age for this study will be significantly lower; specifically all participants will be age 0-18 years. Thus, the results will show the relationship between A1C and covariates at younger ages where identification of at-risk individuals is crucial, as early detection and treatment of the disease has been shown to limit disease progression and physiological damage (Wang, et al., 2011).

Preliminary research calculated the sensitivity, specificity, positive predictive value, and negative predictive value of using the A1C compared to the OGTT in the diagnosis of diabetes and prediabetes. In addition, the preliminary work examined the differences of the results between African Americans, Hispanics, and Caucasians in children, adolescents, and adults. Although the results indicate low sensitivity and positive predictive value for the A1C, negative predictive values range from 92.8-98.3% for diabetes diagnosis and 87.0-97.7% for prediabetes diagnosis (Hitt et al., 2012), using the cut-off points suggested by the American Diabetes Association (ADA, 2012). The significance of the higher negative predictive value is that threshold limits can be established to use A1C testing as a screening tool for additional diagnostic testing. Receiver operator characteristic (ROC) analysis suggests a cut-off of A1C level of 5.6%

for Caucasian and Hispanic individuals and 5.7% for African American when diagnosing prediabetes. By only performing OGTTs on individuals with A1C higher than 5.6% in Caucasian and Hispanic individuals and 5.7% in African Americans, analysis suggests a negative predictive value of 99.1% for individuals with diabetes and 95.2% for individuals with prediabetes (Hitt et al., 2012). By using the A1C test as a screening tool, fewer individuals will need to undergo the OGTT, which is a time-consuming, costly, and poses higher risk to the individual.

Purpose of the Study

The purpose of this study is to establish the accuracy of A1C testing in children and adolescents at-risk for diabetes and prediabetes, identify factors that may alter its accuracy, and determine if a relationship exists between A1C and insulin levels.

Specific Aims and Research Questions

The following were the three specific aims and related research questions of this study:

- **Specific aim 1:** To determine the accuracy of the A1C test to diagnose diabetes and prediabetes in a sample of children and adolescents identified as at-risk for diabetes and prediabetes.
 - 1.1 What is the sensitivity, specificity, positive predictive value, negative predictive value, and ROC curve analysis for the overall sample?
 - 1.2 What is the sensitivity, specificity, positive predictive value, negative predictive value, and ROC curve analysis for each ethnic/racial group (African American, Hispanic, and Caucasian)?
 - 1.3 What are the sensitivity, specificity, positive predictive value, negative predictive value, and ROC curve analysis for each age group (0-5 years, 6-11 years, 12-18 years)?
- **Specific aim 2:** To determine factors influencing A1C that may alter the accuracy of the A1C test to effectively diagnose diabetes and prediabetes in children and adolescents.
 - 2.1 What is the relationship between BMI, family history, age, race/ethnicity, fasting plasma glucose, 2-hour OGTT, and vitamin D levels on the A1C level?
- **Specific aim 3:** To determine the relationship of beta cell function and insulin resistance to A1C in children and adolescents.

- 3.1 What is the correlation between insulin levels and beta cell function during a 2 hour OGTT and A1C results?

Operational Definitions

Adolescent is an individual who is older than 12 years (144 months) of age but younger than 18 years (216 months) of age at the time of the diagnostic testing.

Beta Cell Dysfunction is a condition which the beta cells of the pancreas fail to produce sufficient insulin. The severity of beta cell dysfunction is measured by insulin levels (ADA, 2014)

Body Mass Index (BMI) is a score calculated by the participant's height and weight. For the purpose of this study, it was used to approximate body mass and to identify participants who were overweight or obese.

Child is an individual younger than 12 (144 months) years of age at the time of the diagnostic testing.

Diabetes is a metabolic disease characterized by hyperglycemia. For the purpose of this study, it is a classification given to participants with a FPG \geq 126 mg/dl or a 2-OGTT \geq 200 mg/dl, in accordance with the ADA Diagnostic Guidelines (2014). For the purpose of this study T1DM and T2DM were classified the same.

Diabetes Type I (T1DM) is a type of diabetes mellitus that is caused by injury to the beta cells in the pancreas that render the cells unable to produce insulin. For the purpose of this study, ADA (2014) guidelines for diagnosing diabetes will be used. There will not be a differentiation between T1DM and T2DM.

Diabetes Type II (T2DM) is a type of diabetes mellitus that is caused by decreased sensitivity of tissue to insulin. The condition is marked by hyperinsulemia. In later stages of the disease, beta cells become impaired and are unable to produce insulin in the quantities needed for glycemic control. For the purpose of this study, ADA (2014) guidelines for diagnosing diabetes will be used. There will not be a differentiation between T1DM and T2DM.

Fasting Plasma Glucose (FPG) is a lab test that measured the plasma glucose concentrations in participants after at least 8 hours of fasting from food or drink (ADA, 2014).

Gender is either male or female and was participant or guardian-reported.

Glycemic Control is the biological process of controlling glucose concentrations within the body. Glycemic control is an individualized concept, and definitions of control will vary based on the presence of disease. For non-diabetic individuals,

glycemic control is defined as blood glucose concentrations between 70-130 mg/dl pre-prandial, blood glucose concentrations less than 180 mg/dl 2-hours post-prandial, and a A1C level less than 6.5% (ADA, 2014)

Glycated Hemoglobin or A1C (A1C) is a form of hemoglobin that measures the average plasma glucose concentrations over time. The ADA (2014) measures A1C >6.5 % as a positive test for diabetes, whereas A1C between 5.7-6.4% measure as a positive test for prediabetes.

Insulin Resistance is the body's inability to utilize insulin. It was calculated in this study using the quantitative insulin-sensitivity check index (QUICKI). Research suggests a find of <0.3 is equivalent to insulin resistance (Velasquez-Mieyer, et al., 2008).

Oral Glucose Tolerance Test (OGTT) is a test for the diagnosis of diabetes or prediabetes. Serum glucose concentrations are obtained at fasting. After the intake of a 75 gram glucose solution, serum glucose concentrations are tested at 30 minutes, 60 minutes, 90 minutes, and 120 minutes post intake (ADA, 2014).

Prediabetes is a classification given to participants with a FPG 100-125 mg/dl or a 2-OGTT 140-199 mg/dl, in accordance with the ADA Diagnostic Guidelines (2013). Prediabetes is also termed "impaired glucose tolerance".

Race/Ethnicity is based off a participant self-reporting or guardian-reporting on the patient medical record. Participants were classified as African-American, Caucasian, or Hispanic based off of the medical record. Participants identified as multiracial were excluded from the study. Participants with race/ethnicity identified as anything other than African American, Caucasian, or Hispanic were excluded from the study.

Vitamin D is a fat-soluble corticosteroid that plays a role in the development of diabetes. Research is limited to its role, other than some studies that suggest vitamin D deficiency increases the likelihood of diabetes development. Vitamin D levels were tested using the 25-hydroxyvitamin D test. Optimal levels of vitamin D in children and adolescents are 50-75 ng/ml, while levels less than 11 ng/ml are considered deficient (CDC, 2011).

Assumptions

The framework for this study is grounded in the following assumptions:

1. The "gold standard" for the diagnosis of diabetes and prediabetes is the oral glucose tolerance test.
2. Participants fasted from food or drink for a minimum of 8-hours prior to all testing.
3. Laboratory data were obtained and recorded accurately for each participant

4. Participants information retrieved from participant or guardian health interviews was accurately reported.
5. Laboratory tests were collected via standard agency collection policies.

Limitations

The following limitations were identified in the study:

1. Data were obtained from one clinic in the same geographical area. Results may not be generalizable to other areas or to other clinics.
2. A secondary data analysis was performed on a prospective study, which limited particular information from being collected.
3. Normative values for A1C in children and adolescents are not known.
4. Data were obtained only from children and adolescents with noted risk factors for diabetes or prediabetes. Children and adolescents without risk factors for diabetes or prediabetes were not tested.

Conceptual Framework

As outlined in **Figure 1-1**, the developed framework aligns with the study aims, as it connects the known factors influencing glycemic control to diabetes, prediabetes or no-disease. The framework begins with a wheel that identifies factors known to influence glycemic control. The wheel includes the variables that will be examined in the study, specifically, race/ethnicity, age, insulin resistance (insulin levels), vitamin D, and obesity (body mass index). In addition, the wheel includes variables that are not examined in this study, but do impact glycemic control. These shaded variables include physical activity, magnesium deficiencies, family history, diet, autoimmune disorders, hormonal disorders, and infection. The interior of the wheel is connected via arrows, which indicates the variables are connected and have the potential to influence each other.

The wheel points to a see-saw that depicts glycemic control. As glycemic control is a dynamic condition, it is placed on a lever balanced on a fulcrum. To the left of the fulcrum lies the area of disease, which is diabetes or prediabetes. To the right of the fulcrum lies the area of no-disease. Under glycemic control are the diagnostic tests that are used to measure glycemic control, specifically the OGTT and A1C.

The lever/fulcrum system most importantly indicates that the disease process is a dynamic state. Individuals can often move the direction of the lever by adjusting the factors in the wheel. Factors that limit glycemic control will position the lever in favor of disease, while factors that promote glycemic control will position the lever in favor of no-disease. As outlined in the framework, the severity and presence of the disease can be attenuated by the factors in the wheel. Moreover, glycemic control is measured with the gold standard OGTT and the A1C.

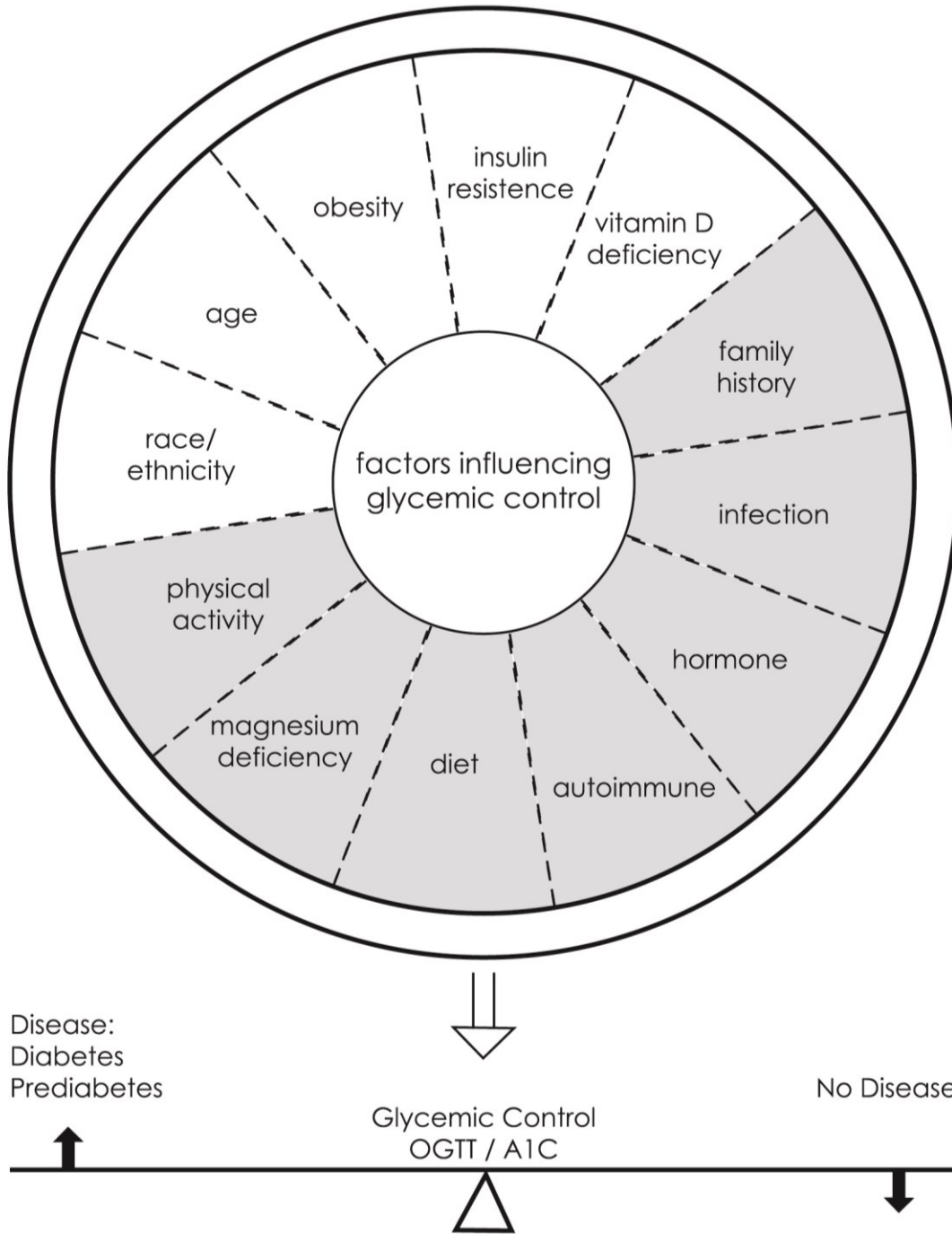


Figure 1-1. Glycemic control concept map

Diabetes

The causes of diabetes are complex. T1DM has a genetic and vitamin D deficiency link, although research shows most often it is caused by autoimmune disorders and/or viral infections that attack beta cells within the pancreas, rendering the beta cells unable to produce insulin and also causing alpha cell dysfunction. As a result of beta cell dysfunction, lipolysis occurs, which stimulates increased glycerol, and gluconeogenesis. Individuals with T1DM develop low insulin levels and are unable to achieve glycemic control without medication (Jones, Brashers & Huether, 2010).

T2DM has a variety of causes, most often directly linked to obesity, physical inactivity, and diet. Impaired insulin release in the pancreas, due to beta cell dysfunction, insulin resistance by muscle tissue, or decreased insulin clearance leads to hyperinsulemia. These individuals may be able to achieve glycemic control via lifestyle medications and diet. However, medication is often required to achieve glycemic control (Jones, Brashers & Huether, 2010).

Testing for diabetes

A full clinical assessment of an individual for diabetes will include a variety of assessments tools, including many laboratory tests. The gold standard used to diagnose diabetes has been the oral glucose tolerance test. Positive fasting plasma glucose or positive 2-hour results will trigger a diagnosis of diabetes or prediabetes. More recent research has suggested high A1C also validate the diagnosis of diabetes (Jones, Brashers & Huether, 2010).

Additional tests are warranted to determine the cause of the disease. These tests include insulin levels, specific antibodies, genetic testing, c-peptide levels, hepatic function, kidney function, triglyceride panels, vitamin D, and magnesium. These tests are not used to diagnose diabetes, but rather are used to identify the cause of the disease (Jones, Brashers & Huether, 2010).

Glycemic control

Glycemic control is achieved in individuals with diabetes primarily through medical intervention, although diet and lifestyle changes can also impact glucose concentrations. Glycemic control is often determined on an individual basis. The conceptual model shows how glycemic control is a dynamic state that is altered with changes in medication, diet, and lifestyle interventions.

Summary

In summary, this chapter provided an introduction to the concept of A1C testing as screening and diagnostic testing for diabetes and prediabetes in children and adolescents. This chapter discussed the purpose, aims, and specific research questions that will seek to identify more clearly the relationship between A1C and various covariates. Chapter 2 will focus on the review of literature for all the proposed research questions, while chapters 3-5 will provide the results and discussion for the proposed research questions.

CHAPTER 2. LITERATURE REVIEW

Introduction

The protocols for screening, diagnosis, and identification of individuals at-risk for diabetes and prediabetes are changing. Past policies focused exclusively on tests that examined glucose in blood serum, such as the fasting blood glucose and 2 hour oral glucose tolerance test (OGTT) (ADA, 2013; ADA 2007). New research has shown hemoglobin A1C assay (A1C) testing to be effective at diagnosing diabetes (Lindstrom et al., 2003; Willis et al. 2007) However, limited evidence exists that demonstrates the effectiveness of using A1C to screen or identify individuals with impaired glucose tolerance (Rohlfing et al., 2002; Stern, Williams, Haffner, 2002). Moreover, research has shown differences in A1C between races after adjusting for covariates (Boltri et al., 2003; Christensen et al., 2010). A review of current literature shows a gap in research concerning the use of A1C for the testing of diabetes and prediabetes in children and adolescents. This review will focus on the A1C as a diagnostic test for diabetes and prediabetes in youth, the relationship of A1C to other factors and potential covariate, and the relationship between A1C and beta cell dysfunction and insulin sensitivity.

Diabetes and Prediabetes Screening Tests

The current standard for the screening and diagnosing of diabetes and prediabetes is the oral glucose tolerance test (ADA, 2013). Current trends have focused on the use of A1C testing to screen and diagnose individuals for diabetes. However, research has shown the A1C test to be accurate and precise for the diagnosis of diabetes only when A1C exceed 6.5% (Cowie et al., 2010; Peter et al., 2007; Wang et al., 2002). Limitations still exist when using the test alone to identify individuals with impaired glucose tolerance. Individuals with levels below 6.5% are generally not diagnosed with diabetes. However these same individuals may be a risk for developing diabetes. Early detection of pre-diabetes could lead to measures to halt disease progression and complications. (McCarter, Hemepe & Chalew, 2006). Early detection of the diseases could lead to implementation of measures to halt disease progression, which could limit the complications of the diseases.

The use of A1C testing to identify individuals at-risk for the development of diabetes has been controversial (ADA, 2007; McCarter, Hemepe, Gomez & Chalew, 2004). The International Expert Committee, appointed by the American Diabetes Association and European Association for the Study of Diabetes, concluded in 2009 that A1C testing can effectively identify individuals at lower risk for developing diabetes mellitus (McCarter, Hemepe, Gomez & Chalew, 2009). However, the committee did warn of limitations regarding the use of the test, including inconsistencies in correlating the A1C test to fasting glucose results, and the overall cost and availability of the A1C test. Moreover, the committee found that the A1C tests do not accurately or precisely diagnose diabetes compared to other tests, such as oral glucose tolerance testing or average glucose concentrations (McCarter, Hemepe, Gomez & Chalew, 2004).

Research studies have pointed to individual differences in the correlation between glucose concentrations and A1C. Cohen, Holmes, Chenier & Joiner (2003) found a higher correlation level ($R^2 > 0.98$) within-person between A1C and fructosamine. This study validated the concept that A1C vary substantially between individuals for a variety of factors, most noticeably due to intracellular glycation. Twin studies further suggest A1C are not entirely associated with glucose concentrations (Sneider et al., 2001; Simonis-Bik et al., 2008; Cohen et al., 2006). Research suggests multiple factors affect A1C, and clinicians should take these factors into consideration when diagnosing and screening for diabetes and prediabetes (Herman & Cohen, 2010).

The strength of A1C testing is that it has been shown to most closely correlate with mean glucose concentrations over time (Nathan, Turgeon & Regan, 2007; Rohlfing et al., 2002). Rohlfing et al. (2002) conducted a pioneer study that analyzed the relationship between plasma glucose and A1C. Using a multicenter, randomized clinical trial, the investigators found a predictable relationship between plasma glucose concentrations and A1C in adults. These findings were later used by the ADA to develop the criteria for the use of A1C as a diagnostic test (ADA, 2012). Nathan, Turgeon & Regan (2007) validated findings from the Rohlfing et al. (2002) study when it found A1C closely correlating to average plasma glucose concentrations. Although the Nathan, Turgeon & Regan (2007) sample was small (N=22), the study used continuous glucose monitoring, which measured interstitial glucose concentrations every 5 minutes for 84 days. This study was also used by the ADA in the development of the criteria for use of A1C testing for prediabetes and diabetes diagnoses.

A1C testing has been shown to be effective in predicting disease development in those with diabetes mellitus, such as the likelihood of developing diabetic retinopathy and nephropathy (Wang et al., 2011). It has also been most closely linked to morbidity and mortality rates in diabetes mellitus (Boltri, Okosun, Davis-Smith & Vogel, 2005). However, the use of A1C with disease prediction methods has yielded mixed results. Some research suggests prediction of diabetes mellitus is best done with challenged oral glucose testing, in addition to A1C testing (Stern, Williams & Haffner, 2002; Peter et al., 2007).

However, research has also validated the use of A1C testing as a screening tool (International Expert Committee Report, 2009). In a multiethnic systematic review of adults, Bennett et al. (2010) found an A1C of greater or equal to 6.1% had a sensitivity of 78-91% and a specificity of 79-84% compared to the oral glucose tolerance test in adults. In contrast, research from the National Health and Nutrition Examination Survey III (NHANES III) showed an A1C greater or equal to 6.5% had a sensitivity of 44% and a specificity of 99%. The International Expert Committee Report (IECR) (2009) purported that no single test can be considered a gold standard. Kramer, Araneta & Barrett-Conor (2010) corroborated the IECR report when they concluded that the use of an OGTT alone would fail to identify high percentages of adults with A1C greater or equal to 6.5%.

A1C in Children and Adolescents

The ADA currently recommends screening for type 2 diabetes in asymptomatic adolescents, if their BMI is greater or equal to the 85% percentile, and the adolescent has 2 or more risk factors for the disease. Risk factors can include family history, at-risk racial/ethnic group, conditions or signs of insulin resistance, small for gestational age at birth, or maternal history of gestational diabetes. The ADA further recommends screening tests to be limited to FPG, due to cost and convenience (ADA, 2013). The International Diabetes Federation (IDF) has yet to endorse the use of A1C testing for adolescents or children, although it has endorsed its use for adults (Nowicka et al., 2011). There is a paucity of research regarding the clinical utility of A1C to detect diabetes and prediabetes in children and adolescents.

Nowicka et al. (2011) provides the most comprehensive study to-date on the use of A1C for the diagnosis of diabetes and prediabetes. In a multiethnic cohort of obese subjects under 18 years of age (N=1,156), the ADA guidelines of a 6.5% A1C underestimated the prevalence of diabetes and prediabetes in adolescents and children. Using receiver-operator curve (ROC) analysis, Nowicka et al. (2011) found that the optimal A1C threshold to identify diabetes in obese children and adolescents was 5.8%, while the optimal threshold for the diagnosis of prediabetes was 5.5%. Although this study did not stratify for racial or ethnic differences in the ROC curves, the study concluded that A1C values may be most useful in screening children and adolescents, but it casts doubt on applying adult diagnostic criteria for diabetes to younger populations.

Lee et al. (2011) validated results from the Nowicka et al. (2011) study, finding low sensitivity (75%) but high specificity (>99%) when using A1C for diagnosing diabetes and prediabetes in adolescents compared to fasting plasma glucose (FPG). Lee et al. (2011) utilized NHANES data for individuals between 12-19 years of age and an adult sample. The positive predictive ability of A1C for prediabetes based on ROC curve analysis was low for both FPG (AUC: 0.61) and 2-hr OGTT post-prandial glucose (AUC: 0.53). However, the lower prevalence of the DM and prediabetes in the childhood and adolescent population made it difficult to correlate adult diagnostic criteria to other populations (Lee et al., 2011)

The correlation between plasma glucose and A1C also has been shown to differ between adults and youth. Ogawa et al. (2012) examined school-aged children (mean age=11.9 ± 2.5 yrs) in Japan (N=298) and found FPG levels were not as highly correlated to A1C, when compared to adult counterparts. In the sample school-age children group, an A1C of 6.5% correlated to a FPG=111.4 mg/dL, while previous research in adults found correlation in adults to be 124.4 mg/dL (Seino et al., 2010). As a result, standardized scales correlating A1C to plasma glucose concentrations should be reanalyzed for children and adolescents.

Factors Influencing A1C

Racial and ethnic factors

Racial and ethnic groups show statistically significant mean differences and variation in A1C in adults and children (Herman, et al., 2007; Herman et al., 2009; Kirk, et al., 2008). Studies have shown variations in A1C among different racial groups, whereas mean plasma glucose concentrations do not vary between racial groups. These results suggest a biological basis for the variability across racial groups with respect to A1C testing (Bonds, et al., 2003; Christensen, et al., 2010; Cohen, 2007).

Kirk et al. (2005) used a meta-analysis (N=21) to examine A1C across minority and ethnic groups. The review concluded that African Americans and Hispanic populations have poorer glycemic control and higher A1C than compared to the non-Hispanic white counterparts. Herman et al. (2007) compared A1C from 5 different racial and ethnic groups. Using an adult sample (N=3,819), the study found A1C were higher in racial and ethnic minorities. The difference in A1C was particularly high among African American and Hispanic subjects. This research concluded that the differences between racial and ethnic groups were consistent across previous research studies.

Herman et al. (2009) further examined the racial and ethnic difference in A1C when compared to mean plasma glucose concentrations. Using a multicenter sample of adults from 11 countries (N=2094), the study found difference between racial and ethnic groups for A1C and 1,5-anhydroglucitol levels, but not for mean plasma glucose concentrations. The research concluded that criteria established for the diagnosis of diabetes based on A1C might be challenging due to inherent differences between racial and ethnic groups (Boltri et al., 2003; Christensen et al., 2010; Herman et al., 2009).

Vitamin D deficiency

Recent research has focused on the role of Vitamin D in diabetes (Takiishi et al., 2010). Vitamin D deficiency has a suspected role in the development of T1DM and in the functional ability of beta cells in T2DM (Badawi, Sayegh, Sadoun, At-Thain, Arora, Hadad, 2014). According to Yiu et al. (2011), there is a significant correlation between vitamin D deficiency and A1C. A prospective study by Forouhi et al. (2008) reported an inverse relationship between vitamin D levels and future insulin resistance. Baseline vitamin D insufficiency was correlated a 10 year risk of increased fasting glucose concentrations, 2 hour-glucose concentrations, and a metabolic syndrome risk factor score. A recent prospective study focusing on youth newly diagnosed with diabetes also reported similar results. Doga et al. (2014) reported 91.9% of newly diagnosed youth with diabetes (n=72) had vitamin D deficiency, whereas only 58.5% of non-diagnosed individuals in the control group (n=42) had vitamin D deficiency (p value=0.01). Bayani et al. (2013) validated previous research when they reported similar findings in vitamin D levels between a group of matched diabetes cases and non-diseased subjects. The mean

concentration of vitamin D in the case group was 18.7 ± 10.2 ng/dl, whereas the mean concentration in the control group was 24.6 ± 13.5 ng/dl ($p=0.002$).

NHANES data indicate vitamin D deficiency in the southern United States is estimated to be 53-76% for non-Hispanic blacks compared to 8-33% for non-Hispanic whites (Looker, et al. 2002). With multiple studies indicating a connection between A1C and vitamin D deficiency, in addition to the knowledge that African Americans often exhibit greater rates of vitamin D deficiencies, a connection could exist between lower vitamin D levels and higher A1C in African Americans.

Age

Evidence suggests age plays a role in the acceleration of the diabetes disease process, with youth experience greater complications and inabilities of glycemic control (Narasimhan & Weinstock, 2014). Limited research has explored the effects of age on A1C. Moreover, ADA guidelines for diabetes and prediabetes diagnosis has been limited to testing in the adult population (ADA, 2014). With regard to youth, evidence suggests puberty plays a role in the development and progression of the disease, as complications are hastened during this timeframe (Cho, Craig, Donaghue, 2014). Additional research is needed to set appropriate A1C level diagnostic cut-offs that more accurately reflect disease state in a youth population.

Lifestyle factors and obesity

Research has supported the concept that multiple metabolic, physiological, and lifestyle factors exist that influence serum glucose and A1C (Maruther et al., 2011). Factors include genetic predispositions to increased plasma glucose and conditions that increase binding affinity between hemoglobin and glucose (Soranzo, et al., 2010). In addition, research has identified factors that explain the difference in A1C between racial and ethnic groups that include lifestyle choices and health disparities (Maruther et al., 2011). Most research focuses on lifestyle choices, such as diet and exercise, and their impact on glucose concentrations. However, little research has focused on the effects of diet and exercise directly on the A1C.

Genetic disposition and family history

Genetic predisposition to higher glucose concentrations in African American and Hispanic groups have been identified, and it is known that naturally higher mean plasma glucose level will inherently lead to a higher A1C level. Soranzo et al. (2010) showed a genetic link that affects the ability of ambient plasma glucose and intracellular cytoplasmic glucose to bind, which increases the ratio of glucose to hemoglobin, thus increasing A1C. The research examined 46,368 nondiabetic adults of European descent. Using a meta-analysis, the research identified 10 genetic loci that are associated with

A1C. Soranzo et al. (2010) recommended a reclassification of diabetes diagnosis based on A1C.

Research has also shown genetic variations that cause non-glycemic changes that also impact A1C. According to Meigs et al., (2002), the heritability of A1C is higher (47%-59%) than the heritability of fasting glucose (34%-36%) and the 2-hour result of the OGTT (33%), results that were validated with the findings of Herman et al. (2009). These results indicate A1C variation between racial groups is not necessarily a result of higher mean plasma glucose rates, but rather a result of binding affinity between the hemoglobin and glucose. Changes in binding affinity have been noted in several medical conditions, including hemoglobinopathies often found in African Americans (Jones, Brashers & Huether, 2010). The higher rates of certain medical conditions in African Americans and Hispanic people have been shown to impact A1C (Soranzo, et al., 2010). African Americans and Hispanic people have noted differences in erythrocyte turn-over and hereditary anemias. In addition, African Americans have higher rates of hemolytic anemias, chronic malaria, and hemoglobinopathies, which can increase A1C (Herman et al., 2009)

Demographics and socioeconomic levels

Research has also focused on the contribution of demographic factors to the higher values of A1C in minority groups. According to Maruther et al. (2011), elevated A1C are a greater reflection of health disparities among different socioeconomic groups. This research suggests that environmental and social factors may ultimately lead to lifestyle choices within in racial and ethnic groups that are correlated to higher glucose concentrations. Several studies further correlated A1C to that of personal demographics, such as body mass index, triglycerides, alcohol use, education, and family history of the disease (Dagogo-Jack, 2010; Selvin, Steffes & Zhu, 2009). These studies concluded that genetic and medical conditions partially contribute to the higher A1C, but socioeconomic difference and lifestyle choices ultimately explain the variance in A1C. However, variables, such as vitamin D deficiency and certain hemoglobinopathies were not fully addressed in this research, could reduce the influence of socioeconomics and lifestyle choices on A1C.

Infection

Evidence suggests infection can be a cause shifts in glycemic control. The body's response to physical or emotional stress during infection can lower the secretion of insulin in the system or increase insulin resistance (Jones, Brashers & Huether, 2010). During times of infection, individuals are more likely to see higher glucose concentrations. Transient states of higher glycemic levels may occur during infection, as the metabolic system is impacted by the infection and subsequent reactions.

Hormones

Hormones have a known influence on glycemic control. Glucagon, a counter regulatory hormone, directly impacts insulin and glucose concentrations (Zander et al., 2002). In addition, gut hormones, such as incretin, play a role in the absorption of glucose through the gastrointestinal system (Holst, 2011). With regard to youth, puberty and hormone shifts have been shown to impact glycemic control and diabetes complications. Growth hormones and insulin-like growth factors impact the composition of body adipose, which increase insulin resistance in some individuals (Cho, Craig & Donaghue, 2014). Evidence suggest hormones can either directly impact the ability of the body to control insulin secretion or insulin sensitivity, or hormones can cause the body to increase adipose tissue, which indirectly impacts glycemic control (Mortensen & Hougaard, 1997).

Magnesium deficiency

Evidences suggest lower levels of magnesium are directly correlated to poorer glycemic control. Galli-Tsinopoulo et al. (2014) examined children and adolescents and found magnesium levels were significantly correlated to A1C greater than 7.5%, which can contribute to more severe complications of diabetes. Dasgupta, Sarma & Saikia (2012) found similar results in an adult population. Subjects with hypermagnesemia and type II diabetes had a mean A1C level of 11.9%, whereas subjects with normal magnesium levels had a mean A1C of 9.8% (p=0.0016). Multiple evidence suggest magnesium plays a role in the control of glucose for individuals diagnosed with diabetes (Kim et al, 2010; Sales & Pedrosa, 2006).

Summary of factors affecting A1C

Research has shown that a variety of factors influence glycemic control and subsequent A1C. Although the impact of the variables differs between T1DM and T2DM, the factors invariably impact both diseases. The progression and severity of the disease is also impacted by these factors. In addition, both modifiable factors, such as BMI, vitamin D levels, magnesium levels, and physical activity, and non-modifiable factors, such as race/ethnicity, age, family history, infection, hormonal, and autoimmune conditions can impact glycemic control.

Beta-cell Function and Insulin Sensitivity in Relation to A1C

β -cell function and insulin sensitivity are key factors in the pathophysiology of prediabetes and diabetes development. Variation in these factors have been noted among different racial and ethnic groups, with Hispanic individuals having greater incidences of β -cell dysfunction, while African American individuals have greater incidences of insulin resistance (Toledo-Corral, Vargas, Goran & Weigensberg, 2012). Limited research exists

that examines the relationship between A1C, β -cell function, and insulin sensitivity in children and adolescents. With the understanding that β -cell function and insulin sensitivity vary between racial and ethnic groups, the relationship between these variables should be further explored to ascertain their impact on A1C.

Methods of beta-cell function and insulin sensitivity measurement

Insulin sensitivity and β -cell function can be measured by direct and surrogate methods. The gold standard for insulin sensitivity measurement is the euglycemic-hyperinsulinemic clamp method. However, the method is a time-consuming and difficult test to perform in large scale screenings and with children and adolescents (Schwartz et al., 2008). Surrogate methods have been developed based on fasting insulin, challenged insulin, fasting glucose, and challenged glucose concentrations. β -cell function can be measured accurately via the insulinogenic index (IGI), which measures insulin concentration at 30 minutes post glucose challenge minus fasting insulin to the glucose measures at similar times (Pacini, Tura, Winzer & Kautzky-Willer, 2005). Other surrogate methods are available. However, a literature review of other methods has shown limited research testing the validity and accuracy of their use.

Measurement in children and adolescents

A small number of studies have examined the accuracy of surrogate measurement tools for the measurement of insulin sensitivity and β -cell function in children and adolescents. A cohort study of 31 children found a high correlation between the QUICKI ($r=0.69$) when compared to the euglycemic-hyperinsulinemic clamp method (Gungor, Saad, Janosky & Arslanian, 2004). Another cohort of 131 children found correlations between fasting insulin, QUICKI and HOMA for Caucasians ($r=0.91$) and African Americans ($r=0.86$) when compared collectively to the euglycemic-hyperinsulinemic clamp method (Conwell, Trost, Brown & Batch, 2004). Schwartz et al. (2008) concluded that surrogate methods correlate strongly (HOMA, $r=0.99$; QUICKI, $r=0.79$) when compare to the euglycemic-hyperinsulinemic clamp method.

It is unclear why variation exists between these studies. However, differences exist with regard to the demographics of each study sample. Age, race/ethnicity, and sample size were not consistent. A research gap exists that fully examines the differences between racial/ethnic groups and age groups (prepubescent versus pubescent) children and adolescents.

A1C correlation to insulin sensitivity and beta-cell function

Insulin sensitivity plays a role in the development of prediabetes and diabetes, in addition to other disorders within the spectrum of metabolic syndrome. However, the role of insulin sensitivity has not been fully explained. Research shows insulin sensitivity is

lower among African Americans when compared to Caucasian or Hispanic counterparts (Bennett et al, 2013). Insulin sensitivity has also been shown to be correlated to the development of metabolic syndrome and cardiovascular diseases (Davis et al., 2012)

Measurements of insulin sensitivity have shown correlation to A1C (Heiana et al., 2012). However, there is a stronger correlation between A1C and β -cell dysfunction than insulin sensitivity measurement indices (Hanson et al., 2000). Kim et al. (2012) also A1C were highly associated with insulin secretion/beta-cell function in a group of Korean adults (N=616, p=0.001). Marini et al. (2011) further found a correlation between higher A1C and beta cell dysfunction, but also identified moderate correlation between A1C and insulin sensitivity in a sample of Italian adults. Future research is needed to determine the degree of correlation among different racial and ethnic groups.

The pathophysiology of the development of prediabetes and diabetes could explain this difference. Insulin sensitivity often decreases first in the progression of T2DM. A worsening of glycemic control would occur when β -cell function fails to compensate for the decrease in insulin sensitivity. An increase in A1C would most likely be seen when β -cell function is not able to counter balance the increase in glucose in the system. The simple pathophysiology of the disease progression could explain the stronger correlation between A1C and β -cell dysfunction.

Summary

Research has shown the benefits and shortcomings of utilizing the A1C test for the diagnosis of diabetes in adults. Little evidence exists supporting the use of A1C of the screening of prediabetes in children or adolescents. However, the utilization of A1C testing for screening purposes has shown promise. Factors have been found to affect A1C, most noticeably racial and ethnic groups have been found to have higher A1C on average, despite having statistically similar 2-hour post prandial glucose concentrations (Herman et al., 2009).

Little research exists that supports the use of A1C testing in children or adolescents for the diagnosis or screening of diabetes or prediabetes. As the criteria for the use of A1C testing has been limited to adult populations, research should be performed on younger populations to properly extrapolate diagnostic criteria. Potential covariate factors, such as BMI, age, race/ethnicity, and vitamin D levels, should be considered and properly evaluated for when considering the use of A1C for the diagnosing of diabetes and prediabetes in youth.

Research has also pointed to a stronger correlation between A1C and beta cell dysfunction, when compared to the correlation between A1C and insulin sensitivity. The strength of this relationship is due to the pathophysiology of the disease progress and the ability of the body to regulate insulin sensitivity until beta cell dysfunction occurs. However, a gap exists in the research that fully explains the strength of the collaboration between beta cell dysfunction and insulin sensitivity to A1C in children and adolescents.

CHAPTER 3. HEMOGLOBIN A1C TESTING VERSUS OGTT IN A SAMPLE OF AT-RISK CHILDREN AND ADOLESCENTS: A COMPARISON STUDY

Introduction

The prevalence of diabetes and prediabetes in children and adolescents in the US is growing exponentially (CDC, 2013). The increased number of younger Americans with the disease is burdening the health care system. Children and adolescents with diabetes and prediabetes are more prone to develop co-morbidities as they age, such as cardiovascular disease, atherosclerosis, kidney disease, and retinopathies (Cho, Craig & Donaghue, 2014). Early identification and subsequent treatment of diabetes and prediabetes is imperative.

The ADA recommends the screening of type 2 diabetes in asymptomatic adolescents if a body mass index (BMI) is greater or equal to 85% and the adolescent has 2 or more risk factors for the disease. Risk factors can include family history, at-risk racial/ethnic group, conditions or signs of insulin resistance, small for gestational age at birth, or maternal history of gestational diabetes. The ADA further recommends screening tests to be limited to FPG, due to cost and convenience (ADA, 2014). The International Diabetes Federation has yet to endorse the use of A1C testing for adolescents or children, although it has endorsed its use for adults (Nowicka et al., 2011). As most research regarding use of A1C for diagnosis or screening has been carried out in adults, a gap exists concerning the predictive ability of the test in children and adolescents.

The American Diabetes Association (ADA) recommends the A1C test as a method of diagnosing diabetes and prediabetes in adults (ADA, 2014). Although research supports the diagnostic accuracy of the A1C test when A1C exceed 6.5%, individuals with impaired and normal glucose tolerance are often misdiagnosed with this test (ADA, 2007; Rohfing, et al., 2002). In addition, A1C results have been shown to vary between ethnic and racial minority groups, with significantly higher A1C observed in Hispanics and African Americans, even after accounting for covariates (Boltri, et al., 2005; Cowie et al., 2010; McCarter, Hempe & Chalew, 2006; Wang et al., 2011). As a result, the use of the A1C test to identify individuals with diabetes or prediabetes has been not been used consistently by clinicians.

The International Expert Committee, appointed by the ADA and the European Association for the Study of Diabetes, concluded that the A1C test can effectively identify adult individuals at lower risk for developing diabetes (ADA, 2009). However, the committee warned of limitations of the test, including inconsistent correlations between A1C and fasting glucose results and concerns about the cost and availability of the test. The committee found that the A1C test does not accurately diagnose diabetes compared to other tests, such as the FPG or OGTT (ADA, 2009). The use of A1c alone to diagnose individuals with diabetes or prediabetes must be translated to meaningful clinical practice.

To determine the accuracy of the A1C test to diagnose diabetes and prediabetes in a sample of children and adolescents identified as at-risk for diabetes and prediabetes, we analyzed data from a sample of children and adolescents seeking care for diabetes and prediabetes testing at an urban endocrinology clinic in the southeastern United States.

Research Design and Methods

A retrospective review of 904 patient electronic medical records in an urban endocrinology clinic was conducted. Two subjects were excluded due to self-identification of multiple races/ethnicities. The A1C, FPG, and OGTT were obtained on the same day using a standardized protocol and central laboratory. Demographic data (age, gender, and race/ethnicity) and A1C, FPG, and OGTT results were retrieved.

The study sample consisted of children and adolescents under the age of 18, who sought care at a single clinic in the southeastern United States. Results from blood analysis, physical examination, and health history were extracted from a database and medical records. Exclusion criteria include self-report of race/ethnicity other than African America, Caucasian, or Hispanic or the self-reporting of multiple racial/ethnic groups.

The current study was approved by the Institutional Review Board of the University of Tennessee Health Science Center. A waiver of consent was obtained and no consent or assent for participation was required from the parents/guardian or patient. A standardized protocol for data collection was used. After an 8-10 hour fast, patients had an intravenous catheter placed for blood draws. Fasting blood samples were drawn for glucose, insulin and A1C. Patients consumed 1.75 grams of dextrose/kilogram of body weight (up to 75 grams). Blood samples were obtained at 30, 60, 90, and 120 minutes during the OGTT for glucose and insulin levels.

All lab analyses were performed by LabCorp. Plasma glucose was measured using an automated glucose oxidase method enzymatic method. Serum immunoreactive insulin ($\mu\text{U/ml}$) was measured by double-antibody radioimmunoassay. A1C was measured using the Roche "Tina-quant" 2nd generation assay which is based on turbidimetric inhibition immunoassay (TINA) of hemolyzed whole blood samples.

Definitions

Diabetes and prediabetes were defined based on the 2014 ADA criteria. Diabetes was diagnosed if FPG was ≥ 126 mg/dl or 2-hour OGTT glucose level was ≥ 200 mg/dl. Prediabetes was diagnosed if the FPG was 100-125 mg/dl or the 2-hour OGTT glucose level was 140-199 mg/dl. A1C were calculated from the first serum glucose draw on the date of visit. Based on the 2014 ADA criteria, a patient was identified as testing positive for diabetes if the A1C was $\geq 6.5\%$ and testing positive for prediabetes if the A1C was

5.7-6.4%. FPG levels were drawn from serum samples following 8-10 hours of patient or parent/guardian self-reported fasting. Based on the 2014 ADA, a patient was diagnosed with diabetes in the FPG was ≥ 126 mg/dl or diagnosed with prediabetes if the FPG was 100-125 mg/dl.

Statistical analysis

We analyzed the role of A1C in the diagnosis of diabetes and prediabetes by use of sensitivity, specificity, positive predictive value, negative predictive value for the overall sample. Analyses were made by race and ethnicity (African American, Hispanic, and Caucasian) and by designated age groups (0-5 years, 6-11 years, and 12-18 years), if possible. The sensitivity, specificity, positive predictive value, and negative predictive value of the A1C diagnostic values for diabetes ($A1C \geq 6.5\%$) and prediabetes ($A1C$ 5.7–6.4%) were calculated using SAS version 9.2.

We compared the predictive ability of the A1C to the FPG and OGTT as continuous variables using Receiver operator characteristic curve (ROC) analysis (1-specificity). The DeLong, DeLong, Clarke-Pearson (1988) methods was used to determine the criterion diagnostic threshold values for diabetes and prediabetes via MedCalc version 12.7. The thresholds were determined by optimal points where sensitivity and specificity were maximized (95% CI).

Results

Test results from 902 subjects were analyzed. Two individuals were eliminated after self-identifying as more than one racial/ethnic group. The sample was predominately African American (70.7%) and female (60.7%). In addition, the BMI of the sample was 33.4 ± 8.12 . The average age of the sample was 11.6 ± 3.32 years.

Table 3-1 summarizes sample characteristics stratified by race/ethnicity and gender.

The prevalence of diabetes based on the OGTT was 1.7% (n=15), whereas the prevalence of diabetes based on A1C values was 2.9% (n=26). The prevalence of prediabetes based on the OGTT was 5.6% (n=51), whereas the prevalence of prediabetes based on A1C values was 54.3% (n=491). Mean A1C was $5.7 \pm 0.5\%$ for the 902 subjects.

A1C and diabetes prediction by race and ethnicity

A1C accurately predicted disease in children and adolescents diagnosed with diabetes via an OGTT. As noted in **Table 3-2**, sensitivity of the A1C test to OGTT was 90.9% for the sample, while specificity was higher at 99.7%. Whereas, positive predictive value was 87.0% and negative predictive values was 99.9% for the sample.

Table 3-1. Sample characteristics: Total and by race and ethnicity

Characteristic	Total	African American	Caucasian	Hispanic
Ethnicity (N,%)	902 (NA)	639 (70.7)	109 (12.0)	154 (17.3)
Male (N,%)	355 (39.3)	249 (38.0)	35 (32.1)	70 (45.5)
Female (N,%)	547 (60.7)	390 (61.0)	74 (67.9)	84 (54.5)
Age (mean±SD)	11.6 ±3.32	11.8 ±3.2	12.2 ±3.2	10.3 ±3.5* [^]
Diabetes-OGTT* (N,%)	15 (1.7)	13 (2.0)	0 (0)	2 (1.3)
Diabetes-A1C* (N,%)	26 (2.9)	23 (3.5)	2 (1.8)	1 (0.6)
Prediabetes-OGTT* (N,%)	51 (5.6)	39 (6.1)	7 (6.4)	5 (3.2)
Prediabetes-A1C* (N,%)	491 (54.3)	401 (62.8)	34 (31.2)	56 (35.9)
A1C (mean±SD)	5.7 ±0.5	5.8 ±0.5	5.6 ±0.3*	5.6 ±0.3*

*Based on 2014 ADA Standards of Medical Care. Diabetes diagnosis with OGTT 2 hr results ≥ 200 mg/dl or OGTT fasting ≥ 120 mg/dl or A1C $\geq 6.5\%$. Prediabetes diagnosis with OGTT 2 hr results 140-199 mg/dl or OGTT fasting ≥ 100 -125mg/dl or A1C 5.7-6.4%. * $p \leq 0.05$ between African American and group with like symbol. [^] $p \leq 0.05$ between Caucasian and group with like symbol.

Table 3-2. Summary of results by race and ethnicity

Condition Group Screened	Sensitivity %	Specificity %	PPV %	NPV %
Diabetes*	90.9	99.7	87.0	99.9
African American	91.0	99.4	76.9	99.8
Caucasian	100	100	100	100
Hispanic	100	100	100	100
Pre-Diabetes*	82.7	44.7	8.6	97.9
African American	92.1	35.9	8.6	98.6
Caucasian	71.4	69.6	13.9	97.2
Hispanic	50.0	63.2	3.6	97.8

*Based on 2014 ADA Standards of Medical Care. Diabetes diagnosis with OGTT 2 hr results ≥ 200 mg/dl or OGTT fasting ≥ 120 mg/dl or A1C $\geq 6.5\%$. Prediabetes diagnosis with OGTT 2 hr results 140-199 mg/dl or OGTT fasting ≥ 100 -125mg/dl or A1C 5.7-6.4%.

The A1C was not able to accurately predict prediabetes compared to an oral glucose tolerance test. Sensitivity and negative predictive values were high, 82.7% and 97.9% respectively. However, specificity and positive predictive value for the sample were low, 44.7% and 8.6% respectively.

When stratified by race, A1C had lower sensitivity, specificity, positive predictive value, and negative predictive value for diagnosing diabetes in African Americans compared to Hispanic and Caucasian counterparts. As noted in table 3-2, Hispanic and Caucasian subjects had 100% sensitivity, specificity, positive predictive value, and negative predictive value when using A1C to diagnose diabetes compared to OGTT. However, these results were skewed by the limited number of diabetes positive via OGTT subjects in these groups (n=2).

Hispanic subjects had lower sensitivity (50.0%) than African Americans (92.1%) and Caucasians (71.4%) when diagnosing prediabetes via A1C; whereas, African Americans subjects had decreased specificity for prediabetes (35.9%) when compared to their counterparts. Positive predictive values were low for all groups, however, markedly lower for African Americans (8.6%) and Hispanic (3.6%) subjects. Negative predictive value for prediabetes diagnosis was higher for African Americans (98.6%) and Hispanic (97.2%) subjects than Caucasian (97.8%) subjects.

ROC curves

ROC curve analyses were performed for the sample and were stratified based on race/ethnicity and age groups. The ROC curve analysis was performed on the overall sample to determine a diabetes criterion threshold, but the analysis was not stratified due to limited positive cases in each racial/ethnic group and age group. ROC curves were also not performed for prediabetes cases on subjects under the age of 12, due to limited positive cases. A summary of all ROC curve analysis results is found in **Table 3-3**.

ROC curve analysis of the aggregate sample determined the criterion threshold for diabetes diagnosis is an A1C level greater than 5.8% (**Figure 3-1**). The area under the curve was 0.763 with a Youden Index 0.4196. This threshold is significantly lower than the 6.5% A1C as recommended by the ADA.

Figure 3-2 shows the A1C criterion threshold for prediabetes diagnosis is greater than 5.6%. The area under the curve is 0.705, with a Youden Index of 0.312. **Figures 3-3, 3-4, and 3-5** show the stratified ROC curve analyses based on race and ethnicity. The African American group has a significantly higher A1C criterion threshold of 5.8%, while the Caucasian and Hispanic groups had lower criterion of 5.5%.

Figure 3-6 shows the ROC curve analysis for prediabetes in subjects 12-18 years of age. The A1C threshold criterion in this group is 5.7%. These findings are also consistent with the ADA recommended guidelines for the diagnosis of prediabetes in

Table 3-3. Summary of ROC curve analysis

Disease/Group	Threshold Criterion	AUC	95% CI	Youden Index
Diabetes				
All	>5.8%	0.763	0.734-0.791	0.4196
Prediabetes				
All	>5.6%	0.705	0.674-0.735	0.3120
African American	>5.8%	0.703	0.665-0.738	0.319
Caucasian	>5.5%	0.807	0.721-0.877	0.4552
Hispanic	>5.5%	0.543	0.460-0.625	0.2685
12-18 years	>5.7%	0.703	0.665-0.738	0.3190

Summary based on DeLong, Delong, Clarke-Pearson method. See DeLong, E.R., Delong, D.M., & Clarke-Pearson, D.L. (1988). Comparing the area under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics*, 44(3), 837-845.

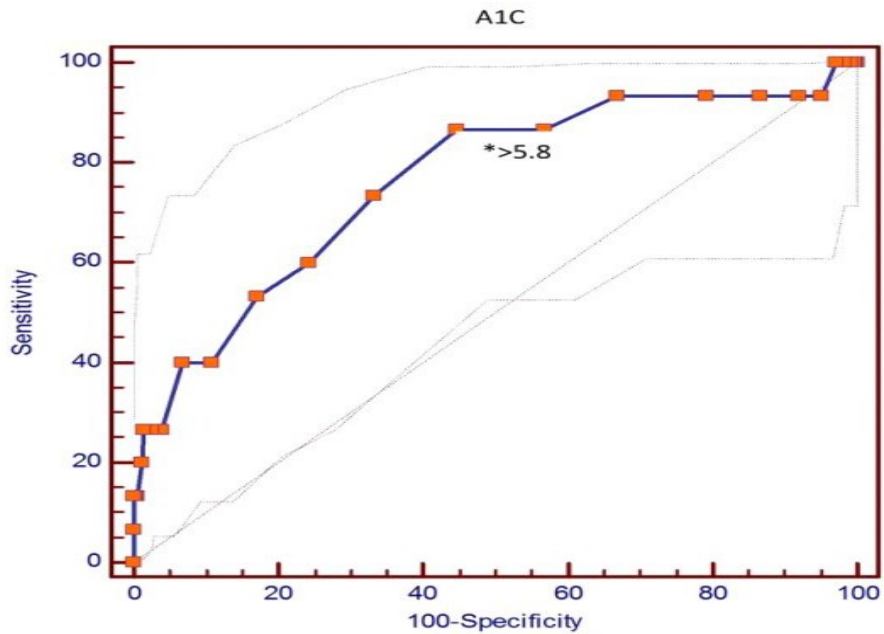


Figure 3-1. ROC curve analysis of diabetes criterion threshold for all subjects

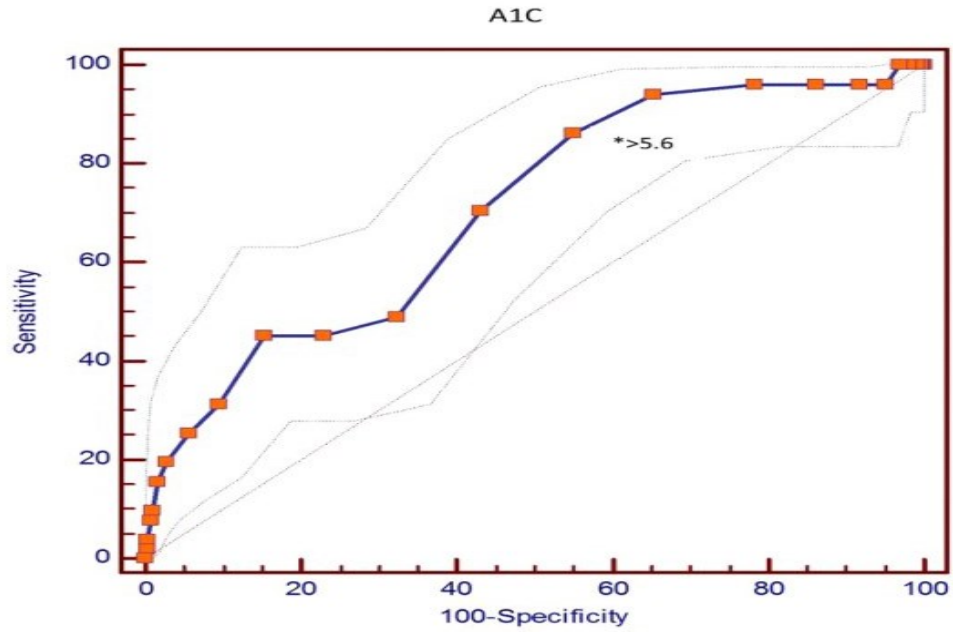


Figure 3-2. ROC curve analysis of prediabetes criterion threshold for all subjects

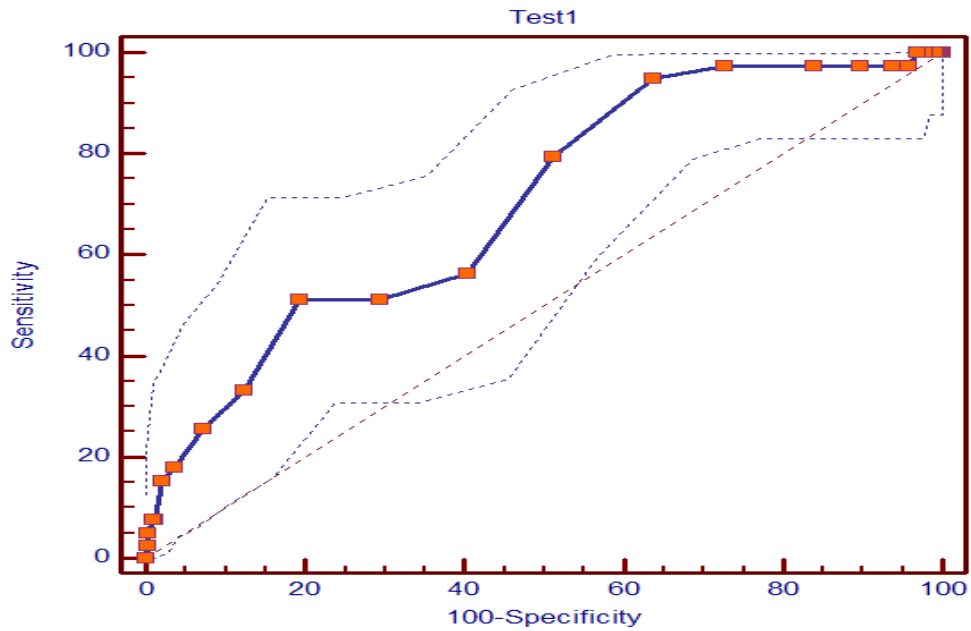


Figure 3-3. ROC curve analysis of prediabetes criterion threshold for African American group

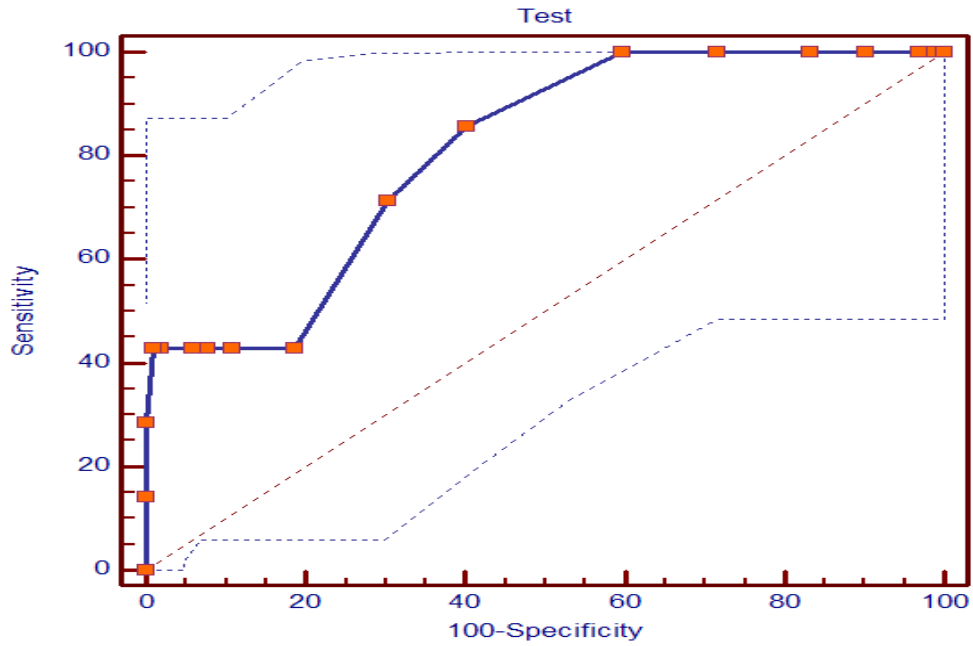


Figure 3-4. ROC curve analysis of prediabetes criterion threshold for Caucasian group.

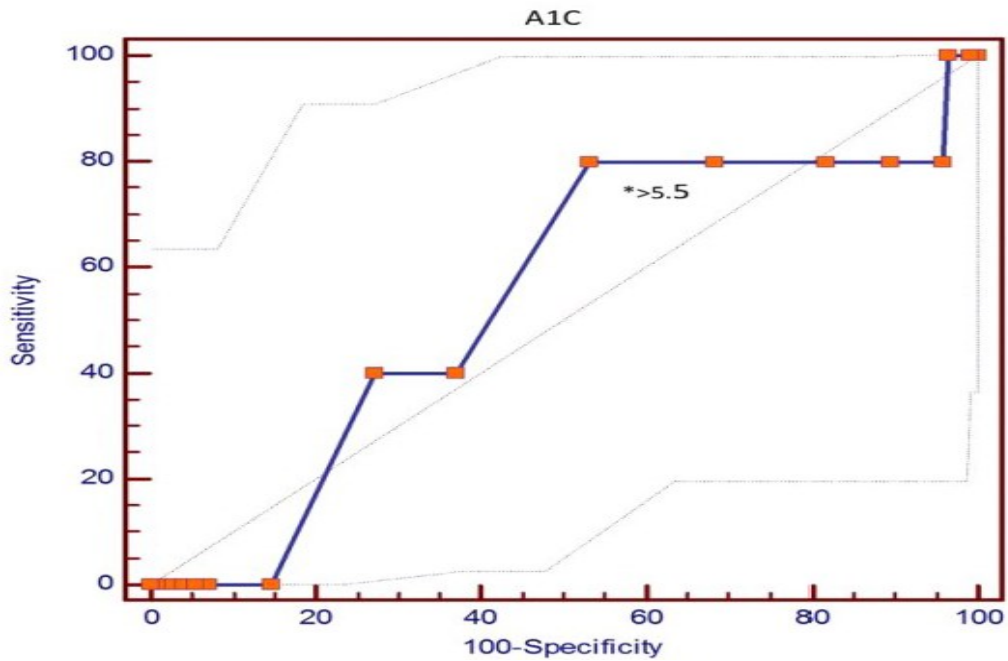


Figure 3-5. ROC curve analysis of prediabetes criterion threshold for Hispanic group

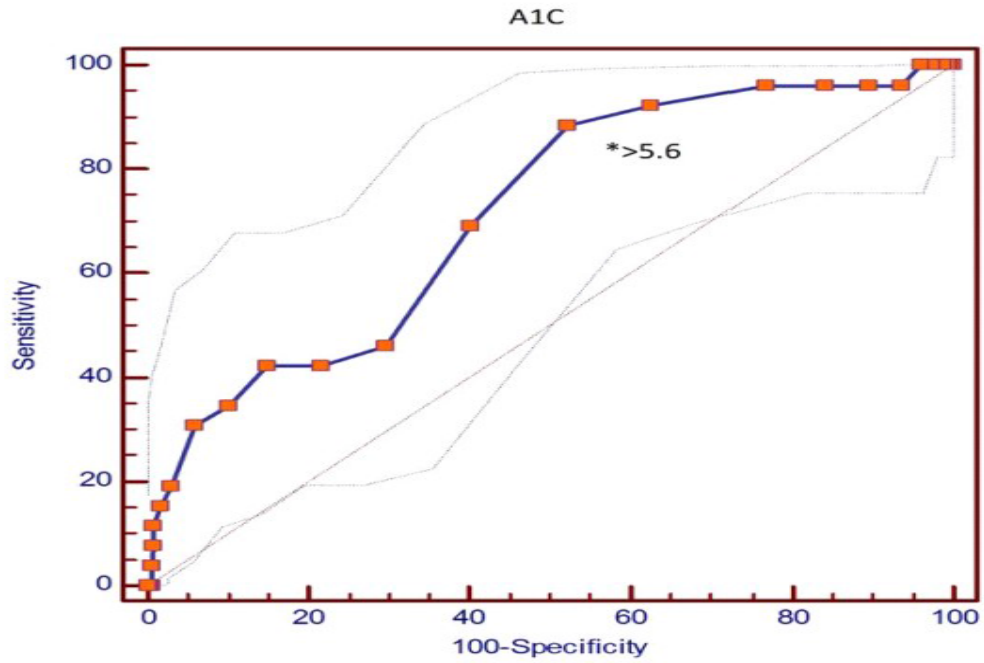


Figure 3-6. ROC curve analysis of prediabetes criterion threshold for subjects age 12-18 years

adults, but is higher than the A1C criterion threshold of the overall sample (5.6%) (ADA, 2014).

Discussion

The A1C test held a high level of specificity and negative predictive value for all ages and race/ethnic groups when testing for diabetes, which indicates the test can successfully identify high-risk individuals without disease. In addition, the specificity and positive predictive value of all groups was high, which indicates some success when identifying high-risk individuals with the disease using the A1C alone.

More caution should be displayed when using the A1C to diagnose prediabetes in all groups. Although the test had a high sensitivity and negative predictive value (82.7% and 97.9%), it showed lower specificity and positive predictive value (44.7% and 8.6%) in successfully diagnosing prediabetes. The A1C test appears to more accurately identify high-risk individuals who does not have prediabetes, but may over diagnose children and adolescents with prediabetes if used alone.

In high-risk children and adolescents in a nonfasting state, the A1C test could be used as a screening device to identify individuals needing OGTT. Current recommendations by the ADA call for diabetes testing of asymptomatic adolescents if BMI is greater or equal to 85th percentile, and the adolescent has 2 or more risk factors for the disease. However, the testing is limited to FPG due to cost and time constraints. The A1C could be used as alternate screening test for children and adolescents to identify individuals needing the more invasive OGTT.

Given that many children with lower BMI levels are now testing positive for prediabetes and diabetes (CDC, 2013), the test could be expanded to children with BMI levels below 85% or with no symptoms. The A1C test could be used as a screening test annually for children and adolescents deemed at high-risk for disease development. Since the test requires no fasting and can be performed with a venous puncture, the use of the A1C test could be used to screen successfully all children and adolescents for the diseases. In addition, the A1C could be used to screen children and adolescents with one or more risk factor for diabetes or prediabetes.

Criterion thresholds for each race and ethnic group and age group of similar characteristics should be considered. African American children and adolescents should use a threshold of 5.8% for prediabetes screening purposes, whereas Caucasian and Hispanics children and adolescents should use a lower threshold (5.6-5.7%). For African American children and adolescents, the use of lower criterion thresholds may results in later stage diagnoses, which delays the initiation of preventative measures. Clinicians should take into account that adolescents overall A1C followed thresholds similar to ADA recommendations for adults. However risk factors and race/ethnicity should be considered at all times when using the A1C as a screening tool. The study noted only 8 false negatives for prediabetes diagnosis in the sample, and none for diabetes diagnosis.

Clinicians should consider the use of serial A1C testing or OGTT in children with multiple risk factors for prediabetes or diabetes.

Performing OGTT on high-risk children and adolescents after positive A1C testing, rather than based solely on risk factors, could provide a cost savings to the health care consumer. This study showed the A1C could accurately identify children or adolescents at low-risk for prediabetes. Using the A1C and risk factors as a screening tool for the more costly and time consuming OGTT, could save the consumer in cost, in addition time and resources.

Limitations of the study include the small number of subjects testing positive for diabetes. The subjects were referred to the clinic often following previous office visits with primary care providers. The majority of cases of diabetes were found via FPG on previous visits. A higher number of diabetes positive subjects were needed to carry out ROC curve analysis on all age groups to determine A1C optimal cut-off points for diabetes. In addition, the BMI of the sample was not representative of the population. The average BMI was 33.41 ± 8.12 . The sample consisted mainly of overweight and obese children and adolescents. The study needs to be replicated with children and adolescents across the BMI spectrum to validate results.

The study also applied only to diagnostic testing by OGTT (either the FPG or 2 hr value). Many clinicians use the FPG alone when screening children and adolescents for diabetes or prediabetes. Research has shown the FPG is not reflective of postload glucose concentrations (Monnie et al., 2003). Comparing the A1C to the FPG alone could reflect differences in screening abilities. A prospective study is needed to compare the use of A1C to FPG testing.

Similar to other studies (Nowicka et al., 2011; Lee et al. 2011) our results support the need for A1C specific thresholds for determination of prediabetes. In our multi-ethnic sample of predominantly overweight and obese youth, the ADA guidelines of A1C > 6.5% for the diagnosis of diabetes underestimated diabetes. Using ROC analyses, the optimal A1C threshold to identify diabetes in our sample was 5.8%. These findings are consistent with results reported by Nowicka et al. (2011) showing that 5.8% was the optimal A1C threshold to identify type 2 diabetes in multi-ethnic cohort of obese children and adolescents.

Similarly, Lee et al. (2011) found low sensitivity (75%) but high specificity (>99%) when using A1C for diagnosing diabetes and prediabetes in adolescents compared to FPG. Utilizing NHANES data for individuals between 12-19 years of age and an adult sample the ability of A1C to predict prediabetes based on ROC curve analysis was low (ROC: AUC: 0.61 diagnosis based on FPG and AUC: 0.53 diagnosis based on 2 hr OGTT). The lower prevalence of diabetes and prediabetes in the childhood and adolescent population make it difficult to correlate A1C adult criteria to other populations. While A1C values may be useful in screening children and adolescents, applying adult criteria to younger populations greatly underestimated the cases of diabetes and prediabetes.

The use of A1C as a diagnostic or screening tool for children or adolescents requires further testing and validation to effectively identify optimal levels. However, the cost and ease of administering the test compared to the OGTT, could provide an alternate means of diagnosing prediabetes or diabetes in younger populations. In addition, the prior research has shown the A1C is superior in diagnostic and screening value compared to the FPG, which is commonly used by clinicians.

In summary, the A1C can be successfully used to screen for prediabetes or diabetes in a population with risk factors for the disease. Additional testing is needed to establish optimal threshold values for children and adolescents with normal BMI and no risk factors. In addition, care should be used when evaluating current recommended optimal criterion thresholds, as racial/ethnic differences are noted.

CHAPTER 4. FACTORS AFFECTING HEMOGLOBIN A1C IN THE DIAGNOSIS OF DIABETES AND PREDIABETES IN CHILDREN AND ADOLESCENTS

Introduction

The American Diabetes Association currently recommends screening for type 2 diabetes in asymptomatic adolescents, if their BMI is greater or equal to the 85% percentile, and the adolescent has 2 or more risk factors for the disease. Risk factors can include family history, at-risk racial/ethnic group, conditions or signs of insulin resistance, small for gestational age at birth, or maternal history of gestational diabetes. The ADA further recommends screening tests be limited to FPG, due to cost and convenience (ADA, 2013). The International Diabetes Federation has yet to endorse the use of A1C testing for adolescents or children, although it has endorsed its use for adults (Nowicka et al., 2011). There is a paucity of research regarding the clinical utility of A1C to predict diabetes and prediabetes in children and adolescents.

The correlation between plasma glucose and A1C also has been shown to differ between adults and youth. Ogawa et al. (2012) examined school-aged children in Japan (N=298) and found FPG levels were not as highly correlated to A1C, when compared to adult counterparts. Seino et al. (2010) found similar results in school-age children group, with an A1C of 6.5% correlated to a FPG=111.4 mg/dL. Similar research shows standardized scales correlating A1C to plasma glucose concentrations should be reanalyzed for children and adolescents.

Research has yet to consistently examine the effects of various factors on A1C in children and adolescence. As noted in **Figure 1-1**, a variety of factors influence glycemic control and subsequently A1C. This study will examine BMI, race/ethnicity, age, gender, insulin sensitivity, β -cell function to determine their influence on A1C. While it is widely accepted that beta cell dysfunction is a known contributor to increased A1C, the contribution of various factors to the A1C in children and adolescents has not been fully explored.

Racial and ethnic factors

Racial and ethnic groups show statistically significant mean differences and variation in A1C (Herman, et al., 2007; Herman et al., 2009; Kirk, et al., 2008). Studies have shown variations in A1C among different racial groups, whereas mean plasma glucose concentrations do not vary between racial groups. These results suggest a biological basis for the variability across racial groups with respect to A1C testing (Bonds, et al., 2003; Christensen, et al., 2010; Cohen, 2007).

Kirk et al. (2005) concluded that the differences between racial and ethnic groups were consistent across previous research studies, after adjusting for covariates. Herman

et al. (2007) also compared A1C from 5 different racial and ethnic groups. Using an adult sample (N=3,819), the study found A1C were higher in racial and ethnic minority after adjusting for other covariates. The difference was particularly high among African American and Hispanic subjects. Herman et al. (2007) concluded caution should be taken when using A1C to diagnose diabetes in certain minority groups.

Herman et al. (2009) further examined the racial and ethnic difference in A1C when compared to mean plasma glucose concentrations. Using a multicenter sample in 11 countries (N=2094), the study found difference between racial and ethnic groups for A1C and 1,5-anhydroglucitol levels, but not for mean plasma glucose concentrations. The research suggests criteria established for the diagnosis of diabetes based on A1C might be challenging due to inherent differences between racial and ethnic groups (Herman et al., 2009).

BMI and lifestyle

Research has supported the concept that multiple metabolic, physiological, and lifestyle factors exist that influence serum glucose and A1C (Maruther et al., 2011). Research also has identified factors that explain the difference in A1C between racial and ethnic groups that include lifestyle choices and health disparities (Maruther et al., 2011). Most research focuses on lifestyle choices, such as diet and exercise, and their impact on glucose concentrations. Obesity is a known risk factor for the development of diabetes and prediabetes in children and adolescents, as a positive correlation is seen between BMI and the presence of the disease (ADA, 2014). However, little research has focused on the effects of diet and exercise directly on the A1C.

Age

Little research exists that examines factors influencing A1C in children or adolescents. Cho, Craig & Donoghue (2014) determined puberty marked a significant shift in glycemic control and diabetes complications. As the start of puberty varies between individuals, it is difficult to ascertain when puberty and age begin to affect glycemic control for an individual. Mortenson & Hougaard also noted that individuals with earlier onsets of puberty have an increased risk for developing prediabetes or diabetes. As the onset of puberty grows increasingly earlier, due to diet and activity levels, age should be evaluated as a possible proxy to the onset of puberty and the possible risk of disease development.

Vitamin D deficiency

Recent research has focused on the role of Vitamin D in diabetes (Takiishi et al., 2010). Vitamin D deficiency has a suspected in role in the development of type 1 diabetes and in the functional ability of beta cells in type 2 diabetes (Zitterman, Alberti &

Shaw, 2001). According to Yiu et al. (2011), there is a significant correlation between vitamin D deficiency and A1C. A prospective study by Forouhi et al. (2008) reported an inverse relationship between vitamin D levels and future insulin resistance. Baseline vitamin D insufficiency was correlated a 10 year risk of increased fasting glucose concentrations, 2 hour-glucose concentrations, and a metabolic syndrome risk factor score.

A recent prospective study focusing on newly diagnosed youth also reported similar results. Doga et al. (2014) reported 91.9% of newly diagnosed youth (n=72) had vitamin D deficiency, whereas only 58.5% of non-diagnosed individuals in the control group (n=42) had vitamin D deficiency (p value=0.01). Bayani et al. (2013) validated previous research when it reported similar findings between a group of matched diabetes cases and non-diseased subjects. The mean concentration of vitamin D in the case group was 18.7 ± 10.2 ng/dl, whereas the mean concentration in the control group was 24.6 ± 13.5 ng/dl (p=0.002).

NHANES data indicate vitamin D deficiency in the southern United States is estimated to be 53-76% for non-Hispanic blacks compared to 8-33% for non-Hispanic whites (Looker, et al. 2002). With multiple studies indicating a connection between A1C and vitamin D deficiency, in addition to the knowledge that African Americans often suffer greater rates of vitamin D deficiencies, a connection could exist between lower vitamin D levels and higher A1C in African Americans.

Beta-cell function and insulin sensitivity in relation to A1C

β -cell function and insulin sensitivity are key factors in the pathophysiology of prediabetes and diabetes development. Variation in these factors have been noted among different racial and ethnic groups, with Hispanic individuals having greater incidences of β -cell dysfunction, while African American individuals have greater incidences of insulin resistance (Toledo-Corral, Vargas, Goran & Weigensberg, 2012). Limited research exists that examines the relationship between A1C, β -cell function, and insulin sensitivity in children and adolescents. With the understanding that β -cell function and insulin sensitivity vary between racial and ethnic groups, the relationship between these variables should be further explored to ascertain their impact on A1C.

Insulin sensitivity and β -cell function can be measured by direct and surrogate methods. The gold standard for insulin sensitivity measurement is the euglycemic-hyperinsulinemic clamp method. However, the method is a time-consuming and difficult test to perform in large scale screenings and with children and adolescents (Schwartz et al., 2008). Surrogate methods have been developed based on fasting insulin, challenged insulin, fasting glucose, and challenged glucose concentrations. β -cell function can be measured accurately via the insulinogenic index (IGI), which measures insulin concentration at 30 minutes post glucose challenge minus fasting insulin to the glucose measures at similar times (Pacini, Tura, Winzer & Kautzky-Willer, 2005). Other

surrogate methods are available. However, a literature review of other methods has shown limited research testing the validity and accuracy of their use.

Measurement in children and adolescents

A small number of studies have examined the accuracy of surrogate measurement tools for the measurement of insulin sensitivity and β -cell function in children and adolescents. A cohort study of 31 children found a high correlation between the QUICKI ($r=0.69$) when compared to the euglycemic-hyperinsulinemic clamp method (Gungor, Saad, Janosky & Arslanian, 2004). Another cohort of 131 children found correlations between fasting insulin, QUICKI and HOMA for Caucasians ($r=0.91$) and African Americans ($r=0.86$) when compared collectively to the euglycemic-hyperinsulinemic clamp method (Conwell, Trost, Brown & Batch, 2004). Schwartz et al. (2008) concluded that surrogate methods correlate strongly (HOMA, $r=0.99$; QUICKI, $r=0.79$) when compare to the euglycemic-hyperinsulinemic clamp method.

It is unclear why variation exists between these studies. However, differences exist with regard to the demographics of each study sample. Age, race/ethnicity, and sample size were not consistent. A research gap exists that fully discusses the differences between racial/ethnic groups and age groups (prepubescent versus pubescent) children and adolescents.

A1C correlation to insulin sensitivity and beta-cell function

Insulin sensitivity plays a role in the development of prediabetes and diabetes, in addition to other disorders within the spectrum of metabolic syndrome. However, the role of insulin sensitivity has not been fully explained. Research shows insulin sensitivity is lower among African Americans when compared to Caucasian or Hispanic counterparts (Bennett et al, 2013). Insulin sensitivity has also been shown to be correlated to the development of metabolic syndrome and cardiovascular diseases (Davis, McGraw, Garner, 2012)

Measurements of insulin sensitivity have shown correlation to A1C (Heiana et al., 2012). However, there is a stronger correlation between A1C to β -cell dysfunction than insulin sensitivity measurement indices (Hanson et al, 2000). Kim et al. (2012) also A1C were highly associated with insulin secretion/ β -cell function in a group of Korean adults ($N=616$, $p=0.001$). Marini et al. (2011) further found a correlation between higher A1C and β cell dysfunction, but also identified moderate correlation between A1C and insulin sensitivity in a sample of Italian adults. Future research is needed to determine the degree of correlation among different racial and ethnic groups.

The pathophysiology of the development of prediabetes and diabetes could explain this difference. Insulin sensitivity often decreases first in the progression of the disease. A worsening of glycemic control would occur when β -cell function fails to

compensate for the decrease in insulin sensitivity. An increase in A1C would most likely be seen when β -cell function is not able to counter balance the increase in glucose in the system. The simple pathophysiology of the disease progression could explain the stronger correlation between A1C and β -cell dysfunction.

Research has shown the benefits and shortcomings of utilizing the A1C test for the diagnosis of diabetes. However, little evidence exists supporting the use of A1C for the screening of prediabetes. However, the utilization of A1C testing for screening purposes has shown promise. Factors have been found to affect A1C, most noticeably racial and ethnic groups have been found to have higher A1C on average, despite having statistically similar 2-hour post prandial glucose concentrations (Herman et al., 2009).

Research has also pointed to a stronger correlation between A1C and beta cell dysfunction, when compared to the correlation between A1C and insulin sensitivity. The strength of this relationship could be due to the pathophysiology of the disease progress and the ability of the body to regulate insulin sensitivity until beta cell dysfunction occurs. A gap in research ultimately exists that fully explores the relationship between beta cell dysfunction and insulin sensitivity to A1C in children and adolescence.

Research Design and Methods

A retrospective review of 904 patient electronic medical records in an urban endocrinology clinic was conducted. Two patients were excluded after self-identifying multiple racial/ethnic groups, which resulted in a sample size of 902. The A1C, FPG, OGTT, and insulin levels were obtained on the same day using a standardized protocol and central laboratory. Demographic data (age, gender, and race/ethnicity) and A1C, FPG, OGTT, and insulin level results were retrieved. Family history and BMI were also retrieved from medical records.

The study sample consisted of children and adolescents under the age of 18 (2-18yrs) who sought diagnostic testing and care at a single clinic in the southeastern United States. Subjects were referred for additional testing and care due to one or more risk factor for the development of diabetes or prediabetes, including increased BMI and family history of disease. Results from blood analysis, physical examination, and health history were extracted from a database and medical records. Exclusion criteria include reporting of race/ethnicity other than African America, Caucasian, or Hispanic.

The current study was approved by the Institutional Review Board of the University of Tennessee Health Science Center. A waiver of consent was obtained and no consent or assent for participation was obtained from the parents/guardian or patient. A standardized protocol for data collection was used. After an 8-10 hour fast, patients had an intravenous catheter placed for blood draws. Fasting blood samples were drawn for glucose, insulin and A1C. Patients consumed 1.75 grams of dextrose/kg of body weight (up to 75 grams). Blood samples were obtained at 30, 60, 90, and 120 minutes during the OGTT for glucose and insulin levels.

All lab analyses were performed by LabCorp. Plasma glucose was measured using an automated glucose oxidase method enzymatic method. Serum immunoreactive insulin ($\mu\text{U/ml}$) was measured by double-antibody radioimmunoassay. A1C was measured using the Roche "Tina-quant" 2nd generation assay which is based on turbidimetric inhibition immunoassay (TINA) of hemolyzed whole blood samples. Vitamin D was measured via 25-hydroxy vitamin D assay.

We analyzed the relationship between race/ethnic groups (African American, Caucasian, Hispanic), gender, age, BMI, vitamin D, fasting glucose, and fasting insulin to the A1C. BMI was calculated the equation for BMI calculation [$\text{BMI} = ((\text{mass in pounds}) / (\text{height in inches}^2)) \times 703$]. Pearson correlation testing were performed on individual variable, with significance set at 0.20 or less. Variables with p-values less than or equal to 0.20 were included in the multiple regression model in a backward method. Variables were included in the final model if significance was determined to be less than or equal to 0.05. The analyses were repeated for the separate racial/ethnic groups. A t-test was performed to determine significant difference between the genders. All analyses were performed using SAS version 9.2 (Cary, NC).

A Pearson correlation determined the strength of relationship between A1C and insulin sensitivity and beta cell dysfunction. Fasting insulin (INS0), corrected insulin at 30 minutes post collection (CIR30), and IGI were used as proxy measurements of insulin sensitivity. Corrected insulin sensitivity index (CISI), QUICKI, and HOMA were used as proxy measurements of beta cell function. Equation indices for the tests are listed in **Table 4-1**. Significance was set at 0.05. All analysis was performed using SAS version 9.2

De-identified data were stored on a Microsoft Excel spreadsheet. Gender (1,0) and race/ethnicity (0, 1, 2) were categorized as discreet variables. Descriptive statistics were used to describe demographic characteristics for the participants. Means with standard deviation were calculated for continuous variables. Frequency distributions were calculated for categorical data.

Results

Test results from 902 subjects were analyzed. The sample was predominately African American (70.7%) and female (60.7%). In addition, the BMI of the sample was 33.4 ± 8.12 . The average age of the sample was 11.6 ± 3.32 years. **Table 4-1** summarizes sample characteristics stratified by race/ethnicity and gender.

The prevalence of diabetes based on the OGTT was 1.7% (n=15), whereas the prevalence of diabetes based on A1C values was 2.9% (n=26). The prevalence of prediabetes based on the OGTT was 5.6% (n=51), whereas the prevalence of prediabetes based on A1C values was 54.3% (n=491). Mean A1C at testing was $5.7 \pm 0.5\%$ for the 902 subjects.

Table 4-1. Insulin sensitivity and beta-cell function indices equations

Indices	Equation
CIR30*	$= \frac{I_{30} \times 100}{G_{30} \times (G_{30} - 70)}$ ($I_{30} \mu\text{U/ml}$ = insulin at 30 minutes, $G_{30} \text{ mg/dl}$ = glucose at 30 minutes)
CISI†	$= \frac{10000}{\text{Square Root} [(FI \times \text{FBG}) \times (\text{mean insulin (0-120 min)} \times \text{mean glucose (0-120 min)})]}$ ($FI \mu\text{U/ml}$ = fasting insulin, FBG mg/dl = fasting blood glucose)
HOMA‡	$= 1 / ((\text{FBG}_{\text{mmol}} \times FI_{\mu\text{U/ml}}) / 22.5)$
IGI*	$= \frac{I_{30} - FI}{G_{30} - \text{FBG}}$ ($FI \mu\text{U/ml}$ = fasting insulin, FBG mg/dl = fasting blood glucose, $I_{30} \mu\text{U/ml}$ = insulin at 30 minutes, $G_{30} \text{ mg/dl}$ = glucose at 30 minutes)
QUICKI§	$= (1 / \log FI_{\mu\text{U/ml}}) + \log \text{FBG}$

* Sluiter, W.J., Erkelens, D.W., Terpstra, P., Reitsma, W.D., Doorenbos, H. (1976). Glucose tolerance and insulin release, a mathematical approach. II. Approximation of the peripheral insulin resistance after oral glucose loading. *Diabetes*, 25, 245-249.

† Matsuda, M., DeFronzo, R.A. (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: Comparison with the euglycemic insulin clamp. *Diabetes Care*, 22, 1462-1470.

‡ Yokoyama, H., Emoto, M., Fujiwara, S. (2003). Quantitative insulin sensitivity check index and the reciprocal index of homeostasis model assessment in normal range weight and moderately obese type 2 diabetic patients. *Diabetes Care*, 26, 2426-2432.

§ Uwaifo, G.I., Parikh, S.J., Keil, M., Elberg, J., Chin, J., Yanovski, J.A. (2002) Comparison of insulin sensitivity, clearance, and secretion estimates using euglycemic and hyperglycemic clamps in children. *J Clin Endocrinol Metab*, 87, 2899-2905.

As outlined in **Table 4-2**, a correlation analysis was performed to determine which variables to include in the multiple regression model. Variables with significance less than or equal to 0.20 were included. All race/ethnic groups, gender, BMI, vitamin D level, fasting glucose, and fasting insulin were considered significant.

A multiple regression was then performed. The model chose a nonzero solution for the parameters that were not unique, and a nonzero solution for the variables that were linearly independent of previous variables, and a zero solution for other variables. As a result, the African American group was excluded from the model due to the variable not being full rank and the least-square solutions for the specific parameters not being unique for the group. The African American group produced biased estimates, and was subsequently excluded.

As outlined in **Table 4-3**, the significance for the overall regression model was established at less than or equal to 0.05. The Hispanic group, Caucasian group, and fasting glucose were determined to be significant, although the R-squared value for the model itself was only 0.098. We determined less than 10% of the variation from these three variables could account for the variation in the model as designed.

The data were then stratified between racial and ethnic groups and the multiple regressions were repeated. As outlined in **Tables 4-4** and **4-5**, gender, fasting glucose, and fasting insulin were found to be significant at 0.20 or less for the African American group. A multiple regression model found only fasting insulin and fasting glucose to be significant at 0.05 or less. However, the R-square for the model was 0.053, which shows the model explains little variation in the A1C level.

As outlined in **Tables 4-6** and **4-7**, age, fasting glucose, and fasting insulin were found to be significant at 0.20 or less for the Caucasian group. A multiple regression model found age, fasting insulin and fasting glucose to be significant at 0.05 or less. The R-square value for this model was 0.288. This model explains significantly more variation in the A1C level, than compared to the African American group. However, the inverse association between A1C and age was weak.

As outlined in **Tables 4-8** and **4-9**, among the Hispanic group, only fasting glucose was found to be significant at 0.20 or less. A simple regression showed the fasting glucose to be significant at 0.039 level. However, the R-square value was only 0.027, which explains little variation in the A1C.

Pearson correlation was performed to examine the relationship between insulin sensitivity and beta cell function to A1C. **Table 4-10** outlines the results. CIRC30, CISI, and QUICKI were significantly negatively correlated, while HOMA was positively correlated with the A1C level. Results indicate A1C is correlated with all beta cell function proxy measurements and correlated to the corrected insulin level at 30 minutes, but not the fasting insulin or insulinogenic index.

Table 4-2. Sample characteristics: Total and by race and ethnicity

Characteristic	Total	African American	Caucasian	Hispanic
Ethnicity (N,%)	902 (NA)	639 (70.7)	109 (12.0)	154 (17.3)
Male (N,%)	355 (39.3)	249 (38.0)	35 (32.1)	70 (45.5)
Female (N,%)	547 (60.7)	390 (61.0)	74 (67.9)	84 (54.5)
Age (mean±SD)	11.6 ±3.32	11.8 ±3.2	12.2 ±3.2	10.3 ±3.5*
BMI (mean±SD)	33.4 ±8.12	34.9 ±8.2 [†]	33.1 ±7.1*	27.6 ±5.0* [†]
Vitamin D (mean±SD)	18.3 ±6.9	16.7 ±7.5 [†]	24.4 ±8.4*	20.3 ±8.3* [†]
A1C (mean±SD)	5.7 ±0.5	5.8 ±0.5	5.6 ±0.3*	5.6 ±0.3*

* Based on 2014 ADA Standards of Medical Care. Diabetes diagnosis with OGTT 2 hr results ≥ 200 mg/dl or OGTT fasting ≥ 120 mg/dl or A1C $\geq 6.5\%$. Prediabetes diagnosis with OGTT 2 hr results 140-199 mg/dl or OGTT fasting ≥ 100 -125mg/dl or A1C 5.7-6.4%.

* $p \leq 0.05$ between African American and group with like symbol.

[†] $p \leq 0.05$ between Caucasian and group with like symbol.

Table 4-3. Pearson correlation for individual variables to A1C in overall sample

Variable	Coefficient	std Error	t	p-Value
African American	0.226	0.330	6.960	0.00*
Caucasian	-0.144	0.470	-4.394	0.00*
Hispanic	-0.147	0.041	-4.451	0.00*
Gender	-0.052	0.032	-1.552	0.12*
Age	-0.010	0.005	-0.287	0.77
BMI	0.081	0.002	2.431	0.02*
Vitamin D	-0.119	0.002	-3.519	0.00*
Fasting Glucose	0.231	0.002	7.120	0.00*
Fasting Insulin	0.043	0.000	1.340	0.20*

*Variables with significance at <0.20

Table 4-4. Multiple regression model for variables to A1C in overall sample

Model	Coefficient	std Error	t	p-Value
Constant	4.967	0.163	30.419	0.000
Caucasian	-0.204	0.490	-4.168	0.000*
Hispanic	-0.214	0.043	-4.912	0.000*
Gender	-0.026	0.031	-0.852	0.395
BMI	0.000	0.002	0.217	0.828
Vitamin D	-0.002	0.002	-1.033	0.302
Fasting Glucose	0.110	0.002	6.613	0.000*

* Variables with significance at <0.05

** R-square=0.098

Table 4-5. Pearson correlation for individual variables to A1C in African American group

Variable	Coefficient	std Error	t	p-Value
Gender	-0.069	0.041	-1.679	0.094*
Age	-0.004	0.006	-0.637	0.525
BMI	0.002	0.002	0.666	0.505
Vitamin D	-0.003	0.003	-1.053	0.293
Fasting Glucose	0.001	0.002	5.805	0.000*
Fasting Insulin	0.002	0.001	2.420	0.016*

* Variables with significance at <0.20

Table 4-6. Multiple regression model for A1C in African American group

Model	Coefficient	std Error	t	p-Value
Constant	4.955	0.167	29.683	0.000
Gender	-0.043	0.040	-1.061	0.289
Fasting Glucose	0.011	0.002	5.105	0.000*
Fasting Insulin	0.001	0.001	0.681	0.496

* Variables with significance at <0.05

† R-square=0.053

Table 4-7. Pearson correlation for individual variables in A1C in Caucasian group

Variable	Coefficient	std Error	t	p-Value
Gender	0.024	0.068	0.353	0.725
Age	-0.023	0.010	-2.369	0.020*
BMI	-0.001	0.004	-0.256	0.798
Vitamin D	-0.004	0.003	-1.249	0.215
Fasting Glucose	0.016	0.004	4.127	0.000*
Fasting Insulin	0.006	0.001	3.977	0.000*

* Variables with significance at <0.20

Table 4-8. Multiple regression model for Caucasian group

Model	Coefficient	std Error	t	p-Value
Constant	4.779	0.320	14.944	0.000
Age	-0.025	0.009	-2.829	0.006*
Fasting Glucose	0.012	0.004	3.214	0.002*
Fasting Insulin	0.006	0.001	4.303	0.000*

* Variables with significance at <0.05

† R-square=0.288

Table 4-9. Pearson correlation for individual variables in Hispanic group

Variable	Coefficient	std Error	t	p-Value
Gender	-0.024	0.047	-0.520	0.604
Age	0.005	0.007	0.712	0.478
BMI	0.002	0.005	0.342	0.733
Vitamin D	-0.002	0.004	-0.451	0.653
Fasting Glucose	0.007	0.003	2.078	0.039*
Fasting Insulin	<0.000	0.000	0.534	0.594

* Variables with significance at <0.20

Table 4-10. Simple regression model for Hispanic group

Model	Coefficient	std Error	t	p-Value
Constant	5.046	0.260	19.420	0.000
Fasting Glucose	0.007	0.003	2.078	0.039*

* Variables with significance at <0.05

** R-square=0.027

Discussion

The results from this study underline the multi-dimensional causes of diabetes and prediabetes and further stress the difficulties in predicting the diseases. Factors influencing glycemic control and A1C vary between individuals and racial/ethnic groups and, in some racial groups, among genders. Previous attempts to examine these factors have concluded similar results; the causes of diabetes and prediabetes are multifaceted, often individualized, and often difficult to ascertain.

The results did support previous work that found statistically significant differences and variation in A1C among racial and ethnic groups. Herman et al. 2007 and Kirk et al. 2008 suggest biological variations across these groups with respect to testing. This research supports the concept that a biological and possible genetic component is responsible for the variation in A1C.

Further research is needed to more accurately examine the impact of vitamin D on A1C. Forouhi et al. (2008) showed a strong inverse relationship between A1C and vitamin D levels. The average vitamin D level of the sample (n=24.3 ng/ml) is consistent with deficient vitamin D levels. As outlined in **Table 4-11**, ANOVA showed significance differences in vitamin D levels between racial and ethnic groups, which supports previous research. However, the factor lacked variance throughout the aggregate sample when attempting to correlate vitamin D levels and A1C. As a result, statistical analysis was unable to definitively show a relationship between A1C and vitamin D levels.

Age was not significantly associated with A1C among the African American or Hispanic groups, but was weakly and inversely associated in the Caucasian group. On average, the Caucasian group was the oldest (12.2 yrs) compared to their counterparts. The inclusion of younger, prepubescent youths in the study may account for the weak association between A1C and age. Recent research has shown puberty acts as an accelerator for diabetes and prediabetes, due to hormone shifts (Cho, Craig & Donaghue, 2014).

The sample had a higher percentage of females versus males. An independent t-test comparing A1C between males and females showed no statistically significant differences between the gender groups when looking at the aggregate sample. No research was found that supports a significant difference in A1C between genders in

Table 4-11. Pearson correlation: Insulin sensitivity indices and beta-cell function to A1C

Value	A1C	INS0	CIR30	IGI	CISI	QUICKI	HOMA
r-value	1	0.058	-0.069*	0.031	-0.145*	-0.072*	0.070*
p-value		0.081	0.040	0.356	0.000	0.031	0.036
N	902	902	902	902	902	902	902

* Correlation significant at the 0.05 level (2-tailed).

children or adolescence. As a result, this test supports the finding that a difference does not exist in this population.

The research did show a stronger relationship between β -cell function and A1C than insulin sensitivity and A1C. This relationship is consistent with previous research that found similar results. The pathophysiology of the disease process is most likely to explain this relationship. A decrease in insulin sensitivity can be compensated by an increase in β -cell function to a point. At some point, the β -cells will no longer compensate for the lack of insulin sensitivity. It is at this point glycemic control will shift; glucose concentrations and A1C will rise.

The results validate the previous conceptual framework noted in **Figure 1-1**. The conceptual model notes glycemic control and the subsequent A1C result from a variety of factors, including race/ethnicity, insulin resistance, age, gender, vitamin D, and BMI. Family history, infection, hormonal, autoimmune disorders, diet, magnesium deficiency, and physical activity were not included in the study, research suggests these factors impact A1C. Additional research should focus on addressing the factors not addressed in this research study in order to study more fully the factors influencing glycemic control.

The research was limited due to sample characteristics. The sample was predominately overweight and African American. In addition, the sample was predominately deficient in vitamin D (n=24.3 ng/ml). A lack of variance in several factors limited conventional approaches to statistical analysis. Results were required to be stratified by race/ethnicity to obtain results that were not skewed or biased.

In summary, race/ethnicity, fasting glucose, and fasting insulin correlated to A1C in the sample. However, multiple regression provided models that explained little variation in the A1C. Additional variables, such as family history, infection, hormonal status, autoimmune disorders, diet, magnesium deficiency, and physical activity should be tested and possible added to the model to increase the validity of using proxy variables to predict A1C in children and adolescents.

CHAPTER 5. SUMMARY

This study examined the use of A1C testing for the diagnosis of diabetes and prediabetes in a predominately minority sample of children and adolescents at risk for the development of the diseases. The use of A1C versus OGTT testing showed some advantage in the screening process. The test had a high level of specificity and negative predictive value, which indicates it is able to correctly identify disease-free individuals. Multiple regression testing highlighted the complexity of glycemic control, with minimal variation explained by the factors examined. In addition, variation was found among the racial and ethnic groups.

Implications for Clinical Practice

As noted, A1C testing was able to correctly identify individuals in this sample who were disease free. However, it had lower abilities to identify individuals with the disease, as noted by the lower sensitivity and positive predictive value. Using the A1C as a first step screening tool could better identify individuals needing additional diagnostic testing with the OGTT.

The OGTT is a costly and time consume test to perform. It requires fasting, takes multiple serum samples, and takes an average of 4 hours to complete. Adding an annual A1C test as a screening tool to at-risk children and adolescents, could save time and resources by more accurately identify those individuals at risk. By eliminating children with lower A1C, in spite of noted risk-factors, such as obesity, health care providers could focus on children with higher A1C for diagnostic testing.

Children and adolescents without noted risk factors could also be screened annually for A1C. A1C fingerstick testing is available, which is minimally invasive and can be performed outside the clinic setting. Although this testing should be followed up a serum A1C test, it has potential to accurately identify youth needing additional screening in a community setting.

The use of A1C in children and adolescents shows promise as a screening tool for at-risk youths. The sample included only a small percentage of children under the age of 6 years, which made statistical analysis for that age group unfeasible. However, the use of A1C testing showed the ability to apply the test as a screening tool for older youths at risk for the disease based on ADA criteria.

Due to the limited number of children testing positive for diabetes, ROC curve analysis was only performed to test A1C cut-off points for prediabetes. A1C cut offs for Caucasian and Hispanic youths was determined to be 5.6%, which is consistent with the 2014 ADA guidelines. However, the cut-off for the African American group was 5.7%, which indicates African American youths need a higher cut-off or additional screening

when diagnosing a child or adolescent with prediabetes. Additional research is needed to test cut-off points for diabetes diagnosis using A1C.

Research shows glycemic control is multifaceted. Factors affecting glycemic control often manifest differently among racial and ethnic groups, and can even change across a person lifespan. This study validated the concept factors affecting glycemic control are difficult to gauge. Multiple regression analysis was not able to explain variation in different racial and ethnic groups. Although limitations were present which prohibited part of this analysis, it is possible that this variation is so individualized that attempting to predict glycemic control with a set criteria is not possible. Glycemic control may vary too widely between individuals to accurately predict disease with a set of factors.

This study showed A1C are more closely correlated to beta cell function rather than insulin sensitivity. This result is consistent with previous research (Hanson et al., 2000; Heina et al., 2012). It is feasible to assume this correlation is due to the pathophysiological chain of events that occurs during the development of diabetes. When insulin sensitivity is diminished, beta cells often increase function in order to compensate. This compensation results in appropriate glycemic control, until a time that the beta cells are no longer able to function at a high level. Once beta cell function decreases, glycemic control is no longer able to take place, and A1C rise. This response is reflected in the higher correlation between A1C and beta cell function in the study.

Implications for Conceptual Framework

Figure 1-1 outlines the factors affected glycemic control. According to the conceptual framework, glycemic control is a multifaceted concept. Although this research did not examine all available factors affecting glycemic control, several key factors were examined. The results of multiple regression modeling verified the general construct behind the conceptual map; the mechanisms of glycemic control are difficult to predict.

Individuals have varying degrees of ability for glycemic control. One factor is not enough to predict the presence of disease, nor are factors particularly constant from one individual to the other. This variation makes the process of predicting disease presence and progression difficult for the health care provider. Individuals typically have multiple factors influencing glycemic control. Often adjusting one or more factor can impact disease presence or progression, however, individual variability exists

Based on the conceptual framework, health care providers must be cognizant of the various factors, assess for each factor individually, and provide an individualized plan of care for each client. Plans of care must address factors that can be modified and those factors that cannot be modified. Health care providers should be aware that plans must assume the individual nature of the disease and address each patient accordingly.

Implications for Policy

This study shows significant diagnostic ability when using the A1C to determine the need for additional diagnostics testing. Current recommendations by the American Diabetes Association suggest A1C can be used independently from the 2-hour oral glucose tolerance test (OGTT) to diagnose diabetes (ADA, 2014). However, this research suggests low sensitivity for the A1C test when compared to the gold standard, OGTT, and it shows variance between racial and ethnic groups.

This study calculated the sensitivity, specificity, positive predictive value, and negative predictive value of using the A1C compared to the OGTT. In addition, the study examined the differences of the results between African Americans, Hispanics, and Caucasians. Although the results indicate low sensitivity and positive predictive value for the A1C, negative predictive values range from 92.8%-98.3% for diabetes diagnosis and 87.0%-97.7% for prediabetes diagnosis, using the cut-off points suggested by the American Diabetes Association (ADA, 2014). The significance of the higher negative predictive value is that threshold limits can be established to use A1C testing as a screening tool for additional diagnostic testing. Receiver operator characteristic (ROC) analysis suggests a cut-off of Hg A1C level of 5.6% for Caucasian and Hispanic individuals and 5.7% for African American for prediabetes diagnosis. By only performing OGTTs on youths with A1C higher than 5.6% in Caucasian and Hispanic individuals and 5.7% in African Americans, analysis suggests a negative predictive value of 99.9% of individuals with diabetes and 99.8% of individuals with prediabetes. By using the A1C test as a screening tool, fewer youths will need to undergo the OGTT, which is time-consuming, costly, and poses higher risk to the individual.

This research should be presented to the clinicians, stakeholders, and vested associations. Policy change should initially be sought from the association with the greatest stake in the policy (Longest, 2010). Most clinicians follow the American Diabetes Association's Guidelines for Diagnostic Care, which are published annually following extensive reviews of research. This organization is the primary stakeholder for enacting policy change regarding diagnostic testing for diabetes and prediabetes. Additional data on cost-analysis, benefit-harm analysis, and public perception of the policy are needed to show potential benefits to change. By initially lobbying the American Diabetes Association and then the American Academy of Pediatrics, the greatest impact could be met.

This study suggests great promise for future diabetes research and policy formation regarding diagnostic testing. If the research can be replicated in a more representative sample, the process by which individuals are tested for the disease could change. As a result, the process for diabetes diagnosis could be less costly, less time consuming, and be performed with less risk to the individual. An evidence-based policy change supported by national stakeholders could revolutionize the process of diabetes and prediabetes diagnosis.

Limitations

Limitations existed in this study. The sample was retrieved from a database of medical records. All participants within a set time frame were examined. The sample was predominately African American and female. Statistical analysis during multiple regression eliminated the African American group due to estimate biases in the sample. Multiple regression of the entire sample was not possible.

Additional research is needed to examine the research questions with a more representative sample of children and adolescents, including youth not deemed at-risk for the disease according to ADA criteria. In addition, a sample more evenly divided based on age, racial and ethnicity, and BMI could be used in future studies.

Conclusion

Using A1C as a screening tools is a feasible screening measurement tool, but follow up is needed by way of OGTT for diagnosis of disease presence. The test could be used to screen youth for further testing. However, health care providers must exercise clinical judgment when a negative A1C result is found in the presence of multiple risk factors for the disease. Additional diagnostic testing or multiple A1C tests may be employed if clinical judgment or additional risk factors for diabetes or prediabetes indicate the presence of the disease.

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APPENDIX. UTHSC IRB APPROVAL LETTER

THE UNIVERSITY OF TENNESSEE
Health Science Center



Institutional Review Board
910 Madison Avenue, Suite 600
Memphis, TN 38163
Tel: (901) 448-4824

October 24, 2012

Jennifer McGuire Hitt
College of Graduate Health Science
Department of Nursing

Re: 12-02155-XM

Study Title: Factors influencing hemoglobin A1c levels in the diagnosis of diabetes and prediabetes in adolescents and children.

Dear Ms. Hitt,

The Administrative Section of the UTHSC Institutional Review Board (IRB) has received your written acceptance of and/or response dated October 23, 2012 to the provisos outlined in our correspondence of October 15, 2012 concerning the application for the above referenced project.

The IRB determined that your application is eligible for exempt review under 45CFR46.101(b)(4) in that it involves the study of existing data or other materials that are publicly available or the information will be recorded in a way that subjects cannot be individually identified. Informed consent is waived in accord with 45CFR46.116 (d). Your application has been determined to comply with proper consideration for the rights and welfare of human subjects and the regulatory requirements for the protection of human subjects. Therefore, this letter constitutes full approval of your application (version 1.2) for the above referenced study.

This study may not be initiated until you receive approval from the institution(s) where the research is being conducted.

In addition, the request for waiver of HIPAA authorization for the conduct of the study itself is approved. The waiver applies to the medical records of patients at Life Doc aged 18 and under for the period January 1, 2007 and July 31, 2012.

In the event that volunteers are to be recruited using solicitation materials, such as brochures, posters, web-based advertisements, etc., these materials must receive prior approval of the IRB.

Any alterations (revisions) in the protocol must be promptly submitted to and approved by the UTHSC Institutional Review Board prior to implementation of these revisions. In addition, you are responsible for reporting any unanticipated serious adverse events or other problems involving risks to subjects or others in the manner required by the local IRB policy.

Sincerely,

Handwritten signature of Donna L. Stallings in black ink.

Signature applied by Donna L Stallings on 10/24/2012 01:10:42 PM CDT

Handwritten signature of Terrence F. Ackerman in black ink.

Signature applied by Terrence F Ackerman on 10/24/2012 01:13:40 PM CDT

VITA

Jennifer Hitt (born 1979) received a Bachelor's degree in Physics from the University of Mississippi, a Bachelor's of Science in Nursing from the University of Memphis, and a Master's of Science in Nursing from the University of Mississippi Medical Center. She is currently an Assistant Professor of Nursing with the University of Mississippi Medical Center on the Ole Miss campus. She has worked in a variety of patient care settings, including medical/surgical nursing and patient education. She is the current President of the Mississippi Nurses Association and has served as a state representative to the American Nurses Association from 2012-2014. She is a certified as a Nurse Educator with the National League of Nursing. As a doctoral student at UTHSC, Jennifer conducts research in the areas of diabetes and prediabetes screenings. Her doctoral preparation also included directed studies in the areas of advanced statistical methods and epidemiology. Jennifer will graduate with a Doctor of Philosophy with a major in Nursing in December 2014.