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Comparison of Screening Methods for Pre-diabetes and Type 2 Diabetes Mellitus by Race/Ethnicity and Gender

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Race/Ethnicity and Gender

by

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B.S., Biology

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A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA

Abstract

INTRODUCTION/OBJECTIVES: Current screening guidelines for pre-diabetes and type 2 diabetes mellitus note that there are discrepancies in diagnosing the disease using the fasting plasma glucose test, oral glucose tolerance test, and $HbA1_c$ in high-risk populations. The objective of this study is to compare the effectiveness of screening methods for type 2 diabetes mellitus (T2DM) and pre-diabetes by race/ethnicity and gender.

METHODS: Secondary analyses of the National Health and Nutrition Examination Survey (NHANES, 2005-2008) were performed using SPSS 19.0. Screening outcomes were assessed and compared for a sample of n=10,566, NHW, NHB, MA, and Multiracial/other men and women. Analyses included cross tabulations, ANOVA and partial correlations to establish disease prevalence, effectiveness of screenings, and statistical significance.

RESULTS: It was found that the $HbA1_c$ test is comparable in precision, and is correlated with the FPG for racial and ethnic minorities. The specificities for detecting pre-diabetes using the $HbA1_c$ were higher (64-66%) for these groups than by using the standard, FPG screening method (42-49%). There were no strong, significant differences for screening effectiveness for men versus women.

DISCUSSION: This study revealed that the $HbA1_c$ test might be an effective method for screening for pre-diabetes in racial and ethnic minorities instead of the FPG test alone. Screening in high-risk populations will help delay the onset of T2DM, with increased prevention during the pre-clinical phase.

INDEX WORDS: Type II Diabetes Mellitus, Race, Ethnicity, Gender, Fasting Plasma Glucose (FPG), Oral Glucose Tolerance Test (OGTT), $HbA1_c$.

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- Assist with the Center of Excellence for Health Disparities Research grant, which highlights three research projects intervening in issues related to housing, HIV, and child maltreatment.

Acknowledgements

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I. INTRODUCTION

1.1-Background: Diabetes as a Public Health Problem

Diabetes is a metabolic illness that affects 246 million people worldwide, and it is the underlying cause of morbidity and mortality for many other chronic illnesses (World Health Organization, 2011). Globally and especially, in the United States, Type 2 diabetes mellitus (T2DM) accounts for 90% of documented cases. An analysis of healthcare expenditures related to the cost of T2DM projects that, in the U.S., $4.3 trillion will be spent on diabetes treatment by 2017 (Ariza, 2010). In the United States (U.S.), expenditures related to T2DM are $174 billion annually (Ariza, 2010). These costs include the management of complications of the disease, such as blindness, neuropathy, cardiovascular disease, kidney failure, and limb amputations.

Diabetes occurs when a person has blood glucose levels above 100 milligrams per deciliter (mg/dL) on a chronic basis (APHA, 2010 and National Diabetes Information Clearinghouse, 2008). Diabetes mellitus results from two types of endocrine malfunction that increase blood glucose levels: 1) pancreatic beta cells lose the ability to secrete the insulin that enables the body to metabolize glucose (Type 1), or 2) although insulin is secreted, the body's cells become resistant to its effects and glucose is not metabolized (Type 2).

The prevalence of type I diabetes mellitus (T1DM) is about 215,000 children and young adults (less than 18 years of age). T1DM is an autoimmune response in which the body destroys the insulin-secreting, β-cells in the pancreas (Bluestone, 2010). Without insulin, the body cannot metabolize glucose, blood glucose levels rise, and energy is not available to the body.   In the absence of cellular glucose, fatty tissue becomes the alternate source of energy. This process is called diabetic ketoacidosis, and the byproducts (ketones) are poisonous (Eisenbarth GS, 2008).

Insulin therapy has helped to improve the quality of life for those who actively monitor their glycemic levels, which is the measure of glucose in the blood. (American Diabetes Association, 2010).

In the U.S. T2DM affects around 25.8 million people, and is believed to be undiagnosed in around 7 million of the 25.8 million cases. Researchers identified undiagnosed cases using surveys from the Indian Health Services, CDC, NIH, and U.S. Census Bureau, and other large databases (National Center for Chronic Disease and Health Promotion, 2011). Patients that are undiagnosed have not been previously identified as a diabetic or pre-diabetic, yet tests positively for either category (National Center for Chronic Disease and Health Promotion, 2011). Figure 1 displays the national distribution of T2DM in the U.S. for the year 2008. Those with T2DM have the problem of too much insulin or glucose in the blood stream, called hyperglycemia. In this scenario, the pancreas cannot keep up with the demand of insulin metabolism, and this leads to insulin resistance (National Center for Chronic Disease Prevention and Health Promotion, 2011).

T2DM is the seventh-leading cause of death, causes kidney failure, and is the top reason for non-traumatic amputations (National Center for Chronic Disease Prevention and Health Promotion, 2011). High, chronic levels of blood glucose and insulin lead to damage of organs, tissues and nerves. Some chronic conditions associated with T2DM are, hypertension, blindness, neuropathy (nerve damage), kidney disease, and an increased risk of heart disease and stroke (American Diabetes Association, 2011).

This condition is mostly observed in adults, (more than 18 years of age), who tend to have more fatty tissue than children do. However, the rise of obesity, poor nutrition, and sedentary behaviors is increasing the number of children diagnosed with T2DM. It is also

important to note that the prevalence of children with diabetes (215,000) includes cases of T1DM and T2DM.

Type 2 diabetes mellitus involves a complex interaction between genetics and the environment, and there are proximal factors (family and friends) and distal factors (society and norms) that can influence health behaviors (Centers for Disease Control and Prevention, 2009). In T2DM, these interactions often involve genetics, poor diet/nutrition due to the economy, lack of physical activity because of unsafe neighborhoods, or any other combination of prolonged life events.

Figure 1: 2008 Age-Adjusted Estimates of the Percentage of Adults with Diagnosed Diabetes
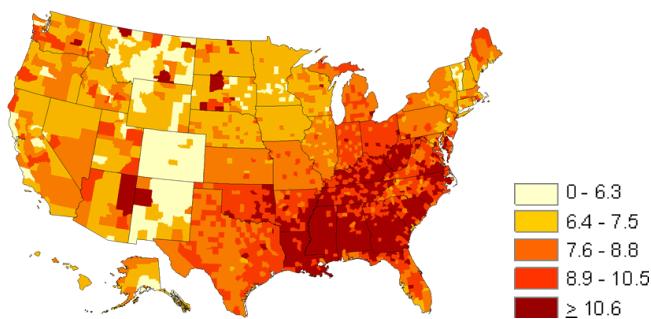
Image adapted from Centers for Disease Control and Prevention: National Diabetes Surveillance System. Available online at: http://apps.nccd.cdc.gov/DDTSTRS/default.aspx. Retrieved 10/4/2011

1.2 - Pre-Diabetes

Pre-diabetes, defined as blood glucose levels above normal but below 126 mg/dL for the fasting plasma blood glucose test (FPG). Pre-diabetes occurs when glycemic levels fall below 199 mg/dL for the oral glucose tolerance test (OGTT) but above normal. Pre-diabetes is the inability to metabolize insulin, and termed "Impaired Fasting Glucose" (IFG) or Impaired Glucose Tolerance (IGT). The categorization of the two depends on the type of glucose test

administered (National Diabetes Clearinghouse, 2008) (see discussion blow). The results of the Diabetes Prevention Program, a large randomized control trial (Diabetes Prevention Program Research Group, 2009), led the ADA, and other medical professionals to advise that pre-diabetics receive greater attention for lifestyle and/or pharmaceutical interventions (American Diabetes Association, 2010).

1.3- Burden of Insulin Resistance for Racial and Ethnic Minorities and Women

Insulin resistance plays a huge role in the disparities seen for the distributions of T2DM for African Americans and Hispanics compared to non-Hispanic Whites (Carnethon, 2002 and Hasson, 2010). Several studies associate chronic hyperglycemia with the high prevalence of T2DM (Ariza, 2010; Marshall, 2007; Dagogo-Jack, 2003). This is due to differences in waist circumference seen in women, which contributes to visceral fat, and is associated with glucose intolerance (Ariza, 2010). Women are also predisposed to insulin resisitance and T2DM, because of GDM and polycistic ovary syndrome (Healthwise, 2009).

There are other risk factors for insulin resistance. Overtime, a sedentary lifestyle can result in excess weight. Additionally, if this weight is concentrated in the midsection of the body, the risk of hypertension is increased and likely to result in insulin resistance. Those that have insulin resistance are likely to develop T2DM if there are no lifestyle changes or medical interventions (National Diabetes Information Clearinghouse, 2008).

 1.4-Methods of Detection

The standard methods for screening for T2DM include the oral glucose tolerance test (OGTT), fasting plasma glucose test (FPG), and the hemoglobin $A1_c$ ($HbA1_c$) test. The American Academy of Family Physicians, American Diabetes Association, and American

College of Obstetrics and Gynecology updated their criteria for screening for T2DM in 2008, based on the recommendations from the United States Preventive Services Task Force (USPSTF) (Norris, 2008). The guidelines recommend (grade B) targeted blood glucose screenings for those with blood pressure ≥ 135/90 mmHg (millimeters of mercury). This will help prevent and slow the progression of cardiovascular complications that accompany hyperglycemia (Marshall, 2007). The consensus is that there is still insufficient evidence regarding the use of targeted screenings for other high-risk populations (recommendation I). There are benefits and disadvantages for each screening method (see discussion below), but here is the standard information regarding the available methods.

The American Diabetes Association (ADA) currently recommends initial screening for T2DM with the fasting plasma glucose (American Diabetes Association, 2010; Norris, 2008) though sensitivity of around 60% is much lower than oral glucose tolerance test (80%). OGTT is the gold standard, yet is typically used in practice for pregnant women to test for gestational diabetes mellitus (Healthwise, 2009). Both test possess room for error, and the $HbA1_c$ method is under continuous evaluation for effectiveness in identifing high-risk populations. This test is currently used in Japan as the initial screening for pre-diabetes, but is not an accepted method worldwide (American Association of Clinical Endocrinologists Board of Directors and American College of Endocrinologists Board of Trustees, 2010). The American College of Endocrinology agrees with the ADA and recommends using the traditional methods versus the $HbA1_c$ because the test is "misleading" in racial and ethnic minority populations, which, again, are high-risk for T2DM and insulin resistance (American Association of Clinical Endocrinologists Board of Directors and American College of Endocrinologists Board of Trustees, 2010).

There are many factors influencing the differential rates of T2DM incidence and prevalence, and the literature suggests the need to intervene in high-risk groups. However, the USPSTF notes that there is not enough evidence for targeted screening (U.S. Preventive Services Task Force, 2008). Futher analysis of the status of health regarding T2DM, pre-diabetes and risk factors associated with acquiring the disease can direct points of intervention for future studies.

1.5- Purpose of Study

The purpose of this study is to examine the rate of detection or screening effectiveness of T2DM and pre-diabetes in high-risk populations using the Fasting Plasma Glucose test (FPG), Oral Glucose Tolerance Test (OGTT), and hemoglobin A1c (HbA1c). While FPG and OGTT are both valid for detecting high glucose concentrations in the blood stream, the $HbA1_c$ test may be more effective for identifying high-risk individuals, such as pre-diabetics. This group can benefit from early detection, and even reverse the onset of illness (Diabetes Prevention Program Research Group, 2009). Exploring screening methods, and comparing their effectiveness over populations using demographics such as race and ethnicity, and gender or sex, will aid in preventing more cases of T2DM in the pre-clinical stage.

1.6-Research Questions

Several studies document that the FPG and OGTT screening methods for T2DM may not be sufficient for properly detecting those who belong to high-risk populations (Colagiuri, 2011, Herman W. H., 2007, and World Health Organization, 2011). Another study shows that event though FPG and OGTT are accepted screening methods, that subtle changes in behavior will alter the results, which leads to misdiagnosing patients (Bisht, 2011). The $HbA1_c$ method is currently used as a tool to moniter the quality of diabetic care a patient recieves, but may be an important tool for more precise screening (Nakagami, 2007). This method currently is not

accepted worlwide because it is more expensive, and runs the risk of misdiagnosing high-risk patients as well (World Health Organization, 2011). This study will use the National Health and Nutrition Examination Survey, 2005-2008, to determine which diabetes screening methods are most effective for racial and ethnic minorites, males and females by comparing several factors. The following questions are considered:

- **Question #1**-- Is there an agreement between the fasting plasma glucose test and $HbA1_c$ against the oral glucose tolerance test for detecting type 2 diabetes mellitus based on race/ethnicity and gender?

- **Question #2**- Is there an agreement between the fasting plasma glucose test and $HbA1_c$ against the oral glucose tolerance test for detecting pre-diabetes mellitus based on race/ethnicity and gender?

- **Question #3**-Are the screening methods effective in detecting pre-diabetes and type 2 diabetes mellitus for all race/ethnicities?

- **Question #4**- Are the screening methods effective in detecting pre-diabetes and type 2 diabetes mellitus for both males and females?

II. REVIEW OF THE LITERATURE

The risk of pre-diabetes and T2DM according to race/ethnicity and gender, and the measurement of that risk, are the research questions in this study. This literature review examines the association of race/ethnicity and gender with diabetes, and briefly introduces common risk factors for T2DM. Descriptions of the accepted screening methods will include descriptions of the process of administering the test, the threshold values for pre-diabetes and T2DM, and benefits and disadvantages of each method.

2.1- Race/Ethnicity

Traditionally, social groups are clustered by racial categories, such as Non-Hispanic Black, Non-Hispanic White, Hispanic/Latino Americans, American Indian, Asian Americans, and Pacific Islander Americans. However, the American Anthropological Association (AAA) has stated that race has no biological plausibility due to physical differences alone (American Anthropological Association, 1998). Ethnicity may be a more realistic construct than race, since those from similar regions possess certain traits that allow them to better adapt and survive in their physical environments (American Anthropological Association, 1998). The term race/ethnicity is now more widely used in the U.S.

Diabetes rates by race/ethnicity

Differences in the rates of obesity are likely a major contributor to the variations in T2DM seen in different racial and ethnic groups. For example, Felicia Hodge and others looked at the health status of morbidly obese women who were American Indians, and found that 34% of the population was obese, a percentage 1.6 times as high as whites (2011). Black women were the only other groups with similar rates of obesity, ranging from 30-37% (Hodge, 2011).

There are several theories regarding these findings. Though hyperglycemia was thought to be the result of increased BMI, one study controlled for BMI and still found that non-obese African American women had a higher glycemic index compared to non-obese white women (Dagogo-Jack, 2003). The thrifty gene theory offers one explanation. Ethnic minorities originating from "hunter-gatherer" nations are thought to possess a "thrifty gene." In times of feast, the body adapted by storing excess insulin/glucose from consumed food for use during times of famine (National Center for Chronic Disease Prevention and Health Promotion, 2011). In modern society where food is plentiful, this characteristic may lead to obesity, which increases the risk of T2DM (Dagogo-Jack, 2003). Minority groups are more likely to report the perception that their health care providers discriminated against them. Those same patients are more likely to report poor health status as opposed to majority social groups (Coreil, 2010).

The National Institutes of Health funded a study as a supplement to the larger study called the Physicians' Understanding of Human Genetic Variation (PUHGV) Study at the Social and Behavioral Research Branch of the National Human Genome Research Institute (Snipes, 2011). The goal was to see how physicians understood the role of genetics and race/ethnicity for the diagnosis and prognosis of T2DM. The study recruited 50 physicians in metro areas around the U.S., and qualitatively assessed whether or not race influenced the way they treated their minority patients. All physicians agreed that patient and family histories are most important to guide treatment and recommendations. Many also believed race/ethnicity to be a risk factor for some conditions (Snipes, 2011). Additional discussions of risk factors associated with race/ethnicity are provided below.

2.2- Diabetes Rates by Gender

Men and women have physiological differences that may put one group over the other for risk of certain health outcomes. It is noted that as of 2010, 13.0 million men have T2DM (11.8%), 12.6 million women (10.8%) do as well. The adiposity or fat distribution is different for men than for women (Dagogo-Jack, 2003). Women that are overweight or obese tend to gain weight centrally, compared to men that gain the weight peripherally (Teixeira-Lemos, 2011). Interestingly, excess adiposity affects men differently than for women. Increasing weight is a risk factor for T2DM, yet is more adverse in women (Paek, 2010). This is due to adiposity around the waist, and circumference of the waist and BMI is a stronger predictor of risk for T2DM in women than in men (Paek, 2010).

Women also have different health-seeking behaviors. Women are more likely to seek the advice of a physician, yet it is less likely they will implement recommended lifestyle improvements (Gavin, 2011). In addition, women who have had children may be more at risk for T2DM if during pregnancy, they had gestational diabetes mellitus (GDM) (American Diabetes Association, 2010). Additional discussions of risk factors associated with gender are provided below.

2.3-Other Risk Factors

Type 2 diabetes mellitus (T2DM) is the result of both genetics and lifestyle behaviors. For example, a diet consisting of mostly high fat, low fiber foods is a risk factor for not only T2DM, but also pre-diabetes and cardiovascular disease. Physical inactivity, low levels of high-density lipoproteins (HDL), family history of diabetes, and hypertension are additional risk factors that health care providers assess while screening for diabetes (American Diabetes Association, 2010). The resolution of T2DM is shown to revert to healthier body and blood

measures through behavior modification (Haas, 2010). By targeting a combination of the risk

factors above and more, health professionals have prevented the on-set of T2DM (Diabetes

Prevention Program Research Group, 2009). The following is an overview of risk factors that are

strong indicators for the disease:

<u>Family History</u>

The association of family history to the risk of T2DM is strong. The ADA reports that the

diagnosis of a parent before the age of 50 results in a 14% increase in risk that their child

develops T2DM (American Diabetes Association, 2011). Other studies have looked for

genes that may contribute to the development of T2DM. Recent work is being done to

identify more mutations, and 18 have been found to affect fasting blood glucose and

insulin levels in healthy adults. Further studies surrounding the gene variations will help

to understand how fasting blood glucose functions, and help diabetics monitor their blood

glucose with precision (Dupuis J, 2010).

Research shows that the mutations are subtle and hard to identify, and only two specific

sequences have been named. These genes are calpain 10 (CAPN10) and hepatocyte

nuclear factor 4 alpha (HNF4A), and belong to the class of single nucleotide

polymorphisms or SNPs (McEntyre, 2004). McEntyre and others believe that the

development of T2DM does not occur without an environmental trigger (2004).

<u>Age</u>

The 65+ years old population is anticipated to double by 2050, which will account for

20% of the U.S. population versus the current 12% (Altpeter, 2010; Centers for Disease

Control and Prevention and The Merck Company Foundation., 2007). Eighty percent of the elderly will have at least one chronic health condition and 50% will have at least two (Centers for Disease Control and Prevention and The Merck Company Foundation., 2007; National Center for Chronic Disease Prevention and Health Promotion, 2010).

Development of T2DM has a long latency period of about 10-12 years, and in 2010, about 26.9% of U.S. residents over the age of 65 years had diabetes (National Center for Chronic Disease and Health Promotion, 2011). This percentage is equivalent to 10.9 million of 25.8 million people with the disease (American Diabetes Association, 2011). The disparity of T2DM complications in older populations is credited to lower glycemic control in African American and Hispanics patients (Weinstock, 2011). Education and income are lower for these two groups than for whites, and these create barriers to awareness of self-care strategies for monitoring glycemic levels.

Socioeconomic Status

Socioeconomic status is a demonstrable risk factor for many chronic health conditions, including T2DM. Education and income directly and indirectly determine the community where a person will live, and affect access to schools, parks, grocery stores, liquor stores, fast food restaurants, and crack houses (Inagami, 2006). Higher education levels are associated with better health outcomes; because this population has typically has a better income, better access to resources that promote health and a better awareness of health-related options (Coreil, 2010).

The Whitehall Studies in the United Kingdom present some of the strongest research on the effects of socioeconomic status on health. These studies followed the health and

social status of a large cohort of British civil servants over time. Workers in the lowest

levels of industry experienced a higher burden of morbidity, and tended to die younger,

than those in upper management did. These outcomes are similar for other studies (Coreil,

2010).

End-stage complications of T2DM, such as renal disease, eye disease, and coronary heart

disease, are often more severe for African Americans and Hispanic/Latino populations

(Ariza, 2010). At least in part, this is due to lack of access to health care, low utilization

of care, and lack of patient self-care (Gavin, 2011). Managing chronic illness can be a

challenge from month to month with low-adherence to medications. This is more likely

when there is not enough income to cover the expense of multiple medications.

Physical Inactivity

Regular physical activity helps regulate glucose levels, blood pressure and help with

weight control, yet most people are physically inactive (Figure 2). Physical activity is

loosely defined as being active for at least 30 minuntes on most days (National Center for

Chronic Disease Prevention and Health Promotion, 2011, Teixeira-Lemos, 2011).

Barriers to physical activity may be the lack of a safe space for recreation in one's

neighborhood, or a pre-existing condition that makes it hard to be physically active.

Though people trust their doctor's advice, research shows that although patients are

advised to increase physical activity, they often do not (Gavin, 2011).

Physical inactivity is most prevalent for women, especially racial and ethnic minorities.

The disparity for physical inactivity in African American and Hispanics women is

initially seen in adolescence. Early on-set of puberty is a possible barrier to physical

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activity, and this health behavior carries into adulthood (Belsky, 2010). It is also noted that men are more likely to engage in physical activity than women (27% versus 25%) are. Also NHB and Latino women were equally more likely to be physically inactive (21%) (Ross C. Brownson, 2005).

A recent study analyzed health behaviors of diabetics in the 2007 the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). The study included whites, blacks and Latinos. Many believed exercise was good for their health, but did not get the recommended time of 30 mins of physical activity on most days. It is also important to note that most people with T2DM are overweight or obese, which may be a barrier to being physically active (Gavin, 2011).

Figure 2: 2008 Age-Adjusted Estimates of the Percentage of Adults Who Are Physically Inactive

Image adapted from Centers for Disease Control and Prevention: National Diabetes Surveillance System. Available online at: http://apps.nccd.cdc.gov/DDTSTRS/default.aspx. Retrieved 10/4/2011

<u>Obesity</u>

Body Mass Index,(BMI= (Weight in Kg/Height in m x height in m)), is a measurement that takes into account a person's height, weight along with lifestyle factors that help to determine the risk for obesity, and the diseases associated with a high value. The units of measurement are kilograms/meter squared (kg/m^2) and values greater than 25 kg/m^2 are overweight. People with a BMI over 30 kg/m^2 are obese. Obesity has become a pandemic, and is attributed to easy access to high caloric, low-nutritional foods, a sedentary lifestyle or being physically inactive most days, low socioeconomics, (Hodge, 2011), and the genetics of race or ethnicity. Also tied to obesity is the fact that the distribution in the waist can indicate a higher risk for T2DM, pre-diabetes, and CVD. Increased adiposity in the waist increases blood pressure and stress on the heart, which can increase damage because of excess blood glucose. In addition to BMI, waist circumference can better predict the risk since BMI can be misleading for those that are athletic.

Huffman and others found an association between waist circumference, BMI, and C-Reactive proteins in Cuban Americans, who are at a higher-risk for T2DM that non-Hispanic Caucasians. The association of C-Reactive Proteins (CRP) levels is the protein markers for low-levels of chronic inflammation. The accumulation of adipose or fatty tissue increases CRP levels. Huffman notes that CRP may be a risk factor for developing DM, and speed the progression of CVD (Huffman, 2010). Increasing physical activity and sustaining an active lifestyle can serve as an anti-inflammatory agent, and prevent T2DM (Teixeira-Lemos, 2011). Figure 3 represents obesity in adults ages 20 and older for 2008.

Figure 3: 2008 Age-Adjusted Estimates of the Percentage of Adults Who Are Obese

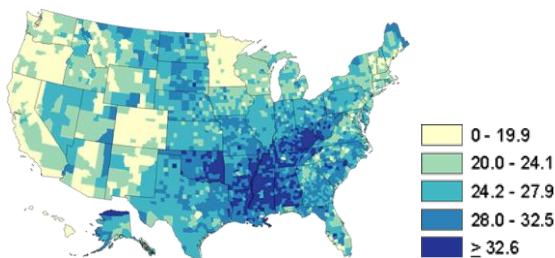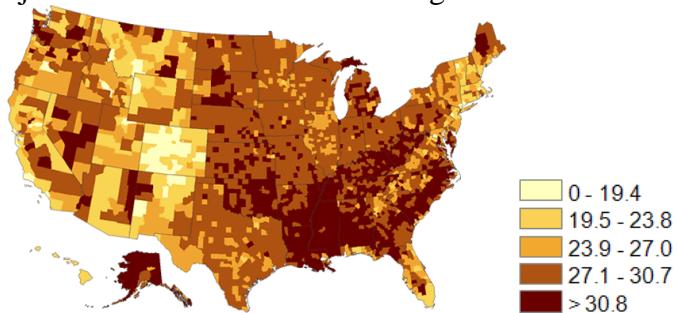

Image adapted from Centers for Disease Control and Prevention: National Diabetes
Surveillance System: Available online
at: http://apps.nccd.cdc.gov/DDTSTRS/default.aspx. Retrieved 10/4/2011.

2.4-Screening Methods for pre-diabetes and T2DM in High-Risk Patients

Oral Glucose Tolerance Test (OGTT)

The "gold standard" for screening for T2DM is the OGTT, because the test is able to

capture around 80% of those who are screened that truly have the disease. The test

requires an eight-hour fast, and then return to the office to drink 75 g of a glucose-rich

liquid. There is a two-hour resting period, and then blood is drawn for analysis. The

threshold for diabetes is a glucose level over 199 mg/dL. Patients with values of 140-199

mg/dL are considered to have Impaired Glucose Tolerance (IGT). Anything below 140

mg/dL is considered normal (American Diabetes Association, 2010).

The test is effective at detecting pre-diabetes and T2DM (American Diabetes Association,

2010). However, some criticisms for the OGTT include the standards for measuring

glycemic indices. The glucose drink challenge does not mimic physiologic response to

glucose metabolism (Borai, 2011). There is intra-individual variability affected by

modifications in diet, exercise, and pre- and post-analysis. For example, anxiety before

the test, illness, consumption of caffeine or alcohol, and changes in exercise and smoking behaviors alters test results (Bisht, 2011). Another issue with OGTT is the reproducibility, or ability to obtain the same reading consistently, is poor (46.6%) for IGT (Agency for Healthcare Research and Quality, 2005).

Fasting Plasma Glucose Test

The FPG is recommended by the ADA as the initial test for screening T2DM, because it is quick and affordable (American Diabetes Association, 2010). They suggest following up with another FPG if there are variations in reading. However, the test has the same issues as the OGTT. Small health behavioral changes may alter readings, and the low specificity (60%) will miss many positive cases. Reproducibility for this test is 17.6%, which is much lower than for OGTT (Agency for Healthcare Research and Quality, 2005).

The process for administering the Fasting Plasma Glucose (FPG) test include an 8-hour fast and a blood sample. A test below 100 mg/dL is considered normal. A test between 100-125mg/dL is considered to indicate higher risk for T2DM, but the threshold for the disease is greater than 126 mg/dL. People in between are said to have Impaired Fasting Glucose or IFG.

Small health behavioral changes may alter readings, and the low specificity (60%) will miss many positive cases (Cosson, 2010). Additionally, the threshold for pre-diabetes (100 mg/dL) is criticized for being too low of a cut point to justify a diagnosis (Schulze, 2009).

<u>Hemoglobin A1c</u>

Recently, WHO and ADA changed their diagnostic criteria and screening methods to include the use of glycated hemoglobin as a more stable detection method. $HbA1_c$, uses cation exchange chromatography, which is able to detect ions on hemoglobin that are found in many diabetic patients. Unlike FPG and OGTT, there is no need to fast, and a small amount of blood is needed to be sampled. (Herman, 2010).

$HbA1_c$ is becoming the more widely accepted, in Japan, Australia, and the United Kingdom because the test is more stable in the preanalytic stage (Nakagami, 2007). Results of the HbA1c test show average concentrations spanning weeks at a time. Unlike glucose tests, short-term lifestyle modifications will not alter the results because patients are not required to fast. Also, the results are not altered by biological variation (Sacks, 2011). These factors affect glucose tests, lower glucose concentration, and can miscategorize patients.

The $HbA1_c$ test measures the percent of glucose in the blood, over the past three months (Colagiuri, 2011). Patients with values greater than 6.4 % are considered diabetic, less than 6.4% but greater than 5.5% are pre-diabetic (Nakagami, 2007). Herman also notes that FGT and OGTT test underestimate glucose levels in those that have pre-existing blood disorders such as anemia, which can be related to ethnicity (2010). $HbA1_c$ is being accepted in practice in the U.S. to moniter glycemic levels in diabetic patients, and measures the quality of diabetic care a patient receives (Centers for Disease Control and Prevention, 2011). Currently, it is not agreed upon whether $HbA1_c$ should be used to

diagnose diabetes (Colagiuri, 2011), yet patient care providers are combining methods of detection for accuracy (2011).

For example, either the FPG or OGTT will be administered to screen for hyperglycemia, and can then be followed up with $HbA1_c$ as a confirmatory test. This is more of a "step-wise method" of screening for pre-diabetes and T2DM (Nakagami, 2007). There are a few problems with this method. It was noted by Herman and Fajans that the Intenational Expert Committee on T2DM recommended against combining methods because of discordant results (2010). An intial FPG test may show that a person has normal values, and the $HbA1_c$ may show that the patient is diabetic. Misclassification can have mental, physical and emotional harms to the patient, which must be weighed in choosing to set $HbA1_c$ as a standard method (U.S. Preventive Services Task Force, 2008; American Diabetes Association, 2010).

Though the $HbA1_c$ has promises to help identify high-risk individuals for T2DM, there have been discprepencies in certain populations. Some populations are predisposed to hemoglobinopathies such as malaria and sickle-cell anemia, which causes hig red blood cell turnover experienced in African Americans. Women tend to have lower values because of conditions of anemia during menstruation, and are at risk for gestational diabetes while pregnant (Herman W. H., 2007).

2.8-Summary

Ongoing research related to type 2 diabetes mellitus translates into focused programming and effective interventions around the nation. Unfortunately, the rise and risk of T2DM is ever increasing with growth of the aging population and high prevalence of obesity and heart disease.

These conditions are co-morbid with T2DM, and place a large burden on the U.S. healthcare system. Prevention through screening is essential for reducing the burden of T2DM for all affected by this chronic condition. It is also important to assess how effective the screening blood plasma glucose tests are for detecting not only diseased cases, but also those with pre-diabetes, who are potential cases. This study will assess the effectiveness of the current methods available. Analysis of the screening methods for pre-diabetes and type 2 diabetes mellitus will help to determine the effectiveness of detecting the disease in high-risk populations.

III. METHODS

This study is based on the cross-sectional analysis of the 2005-2006 and 2007-2008

National Health and Nutrition Examination Survey (NHANES), developed by the National

Center for Health Statistics (NCHS). The study highlights risk factors found in the literature such

as age, gender, body mass index (BMI), height, weight, insulin resistance, and others. Data about

glycemic levels were available from the examinations and laboratories files, which displayed

glycemic measures using the FPG, OGTT and HbA1$_c$ method.

3.1- National Health and Nutrition and Examination Survey (NHANES)

Since the 1960s, the National Health and Nutrition Examination has set the standards for

healthcare practice. The results of the various surveys set policy and guidelines for health

interventions in U.S. populations, such as the growth charts used by pediatricians in clinical

practice, interventions in obesity, and elimination of lead from gasoline in the 1970's. NHANES

data has helped researchers establish trends not only obesity, but also asthma prevalence, and

trends in undiagnosed diabetes. (CDC/National Center for Health Statistics, 2011). The 2007-

2008 version of the survey is the most recent data available for public use. The addition of the

2005-2006 survey adds more power to the study, and provides more reliable estimations of

prevalence and measures of association (CDC/National Center for Health Statistics, 2011).

The surveys and examinations give a cross-section of the status of health for the United

States. Captured in the NHANES questionnaires are prevalence data for the following diseases:

anemia, cardiovascular disease, diabetes, environmental exposures, eye diseases, hearing loss,

infectious diseases, kidney disease, nutrition, obesity, oral health, osteoporosis, physical fitness

and functioning, reproductive history and sexual behavior, respiratory disease, STDs, and vision

3.2- Data Collection and Measures

NHANES conducts in-home surveys and examinations administered in mobile examination centers (MECs) to over 5,000 participants, in over 15 counties across the nation each year. To ensure privacy, respondents use touch screen computers for the computer assisted self-interview (CASI) or audio computer assisted self-interview (ACASI). Results are sent to NCHS within 24 hrs. Trained clinicians performed the examinations, and lab and exam results are stored in a electronic database. This eliminated the need for paper records, and provided another layer of security for participant health information (CDC/National Center for Health Statistics, 2011).

The populations surveyed for the analysis included10, 149 participants for 2007-2008 and 10,348 for the 2005-2006 periods. Certain populations such as Blacks, Hispanics, and those over 60 years were oversampled to make the sample represent the national population. NHANES also aimed to gain more biological information from its aging populations, and researchers purposefully examined and tested more specimens from the group of those 60 years and older (CDC/National Center for Health Statistics, 2011).

The demographics files for 2005-2006 and 2007-2008 were combined to obtain information about each respondent's age, gender, education, income, and race/ethnicity. Data concerning body measures such as height, weight, BMI, systolic blood pressure, and diastolic blood pressure, were taken from examination files. The laboratory files included the results of blood tests for cholesterol, triglycerides, and blood plasma glucose.

Non-Clinical Variables

The study measures obtained from the demographics file needed to be recoded to accommodate the 10,566 respondents. The following are descriptions of how the variables were recoded:

- Age (years): Originally termed, "Age at screening adjudicated-recode", ranged from 0-150 years. The new variable only includes ages 20-80 years of age, and were grouped {1=20-39}, {2=40-59}, {3=60-80} for descriptive purposes.

- Ethnic (independent variable): The original variable termed, "Race/Ethnicity-recode", represented five categories where {1=Mexican American}, {2=Other Hispanic}, {3=Non-Hispanic White}, {4=Non-Hispanic Black}, {5=Multi-racial/Other}. The new variable combined smaller populations to create a larger sample where {1=Non-Hispanic White}, {2=Non-Hispanic Black}, {3=Mexican American}, {4=Multi-racial/Other}.

- Educational Attainment: This variable is created from the "Educational Level-20+" variables with seven categories where {1=less than 9th grade}, {2=9th-11th grade}, {3=HS grad/GED or equivalent}, {4=Some college or AA}, {5=College grad or above}, {7=refused}, {9=don't know}. The new variable combined these categories by level of attainment where 5 was coded as {1=High Educational Attainment}, 3 and 4 were coded as {2=Moderate Educational Attainment}, and 1 and 2 were {3=Low Educational Attainment}.

- Income: This variable is recoded from the "Annual Household Income" measure where, {1=$0-$4,999}, {2=$5,000-$9,999}, {3=$10,000-$14,999}, {4=$15,000-$19,999}, {5=$20,000-$24,999}, {6=$25,000-$34,999}, {7=$35,000-$44,999}, {8=$45,000-$54,999}, {9=$55,000-$64,999}, {10=$65,000-$74,999}, {12=over $20,000},

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{13=under $20,000}, {14=$75,000-$99,999}, {77=refused}, {99=don't know}. The new

variable combined these categories, and used the poverty level for 2005 and 2008 to

determined low-income status ($21,200). Categories 1-5 and 13 were coded {3=Low-

Income}, 6-9 and 12 were coded {2=Middle-Income}, and 14 and 15 were coded

{1=High-Income}.

- Weight (kg): This variable is recoded from the "Weight" variable ranging from 32.4 kg

  (about 70 lbs) to 371.0 kg (about 600 lbs). These cases were compressed into four

  different categories where {1=32.4 kg-83.6 kg}, {2=83.7 kg-164 kg}, {3=165 kg-200

  kg}, and {201 kg-371 kg}.

- Height (cm): This variable is recoded from the "Height" variable ranging from 137.3 cm

  (about 4-ft.4-in.) to 204.1 cm (about 6-ft.7-in). These cases were compressed into four

  different categories where {1=137.3 cm-158.5 cm}, {2=158.6 cm-169.9 cm}, {3=170

  cm-185 cm}, and {4=186 cm-204.1 cm}.

- BMI (kg/m^2): This variable is recoded from the "Body Mass Index ($kg/m**2$)" variable

  ranging from 13.36 kg/m^2 to 130.21 kg/m^2. The values are organized according to the

  CDCs categorizations of body mass indices, where values up to 18.4 kg/m^2 were coded

  {1=Underweight}, values 18.5 kg/m^2-24.9 kg/m^2were coded {2=Healthy Weight},

  values 25.0 kg/m^2-29.9 kg/m^2 were coded {3=Overweight}, and values 30 and above

  were coded {4=Obese}.

Clinical Variables

The combined examination, laboratory surveys and diabetes, blood pressure, HDL cholesterol, LDL cholesterol, and triglyceride questionnaires provide health behaviors regarding medications used, and the presence of risk factors that are co-morbid with T2DM. The following are descriptions of the clinical variables:

- Hypertension: This variable is computed from the "Systolic: Blood pres (2nd reading) mm Hg", "Diastolic: Blood pres (2nd reading) mm Hg", "Systolic: Blood pres (3rd reading) mm Hg", and" Diastolic: Blood pres (3rd reading) mm Hg" to create the mean systolic (MSBP) and mean diastolic blood pressure (MDBP). MSBP, including values greater than or equal to 140 mmHg, MDBP values greater than or equal to 90 mmHg are defined as hypertensive. In addition to the biological measures, answering "yes" to the questions, "Ever told you had high blood pressure?" and "Taking prescription for hypertension?" identified cases that are hypertensive.

- Total Cholesterol (mg/dL): "Total Cholesterol (mg/dL)" is recoded into three categories. Values up to 199 mg/dL were coded {1=Poor}, values including 200 mg/dL up to 239 mg/dL were coded {2=Moderate}, and values of 240 mg/dL and above were coded {3=High}.

- HDL (mg/dL): "Direct HDL-Cholesterol (mg/dL)" is recoded into three categories, which differ for men and women. Values up to 40 mg/dL for men were coded {1=Poor}, values 41 mg/dL up to 59 mg/dL were coded {2=Moderate}, and values of 60 mg/dL and above were coded, {3=High (best)}. For women, values less than 50 mg/dL were coded

{1=Poor}, values 51 mg/dL up to 59 mg/dL were coded {2=Moderate}, and 60 mg/dL were coded {3=High (Best)}.

- LDL (mg/dL): "LDL-cholesterol (mg/dL)" is recoded into three categories with values up to 99 mg/dL coded as {1=Good}, values of 100 mg/dL to 159 mg/dL coded as {2=Moderate}, and values of 160 mg/dL above coded as {3=High}.

- Triglycerides (mg/dL): "Triglyceride (mg/dL)" is recoded into three categories with values up to 149 mg/dL coded as {1=Good}, values of 150 mg/dL up to 199 mg/dL coded as {2=Moderate}, and values 200 mg/dL and above coded as {3=High}.

- Dyslipidemia: This variable is computed from the newly created variables of HDL, LDL, Triglycerides, and answering yes to the questions "Doctor told you - high cholesterol level?" and "Now taking prescribed medicine (for high cholesterol)?".

- Impaired Glucose Tolerance (mg/dL): This variable is computed by selecting cases if the value for the variable "OGTT (200 mg/dL)" is between 140 mg/dL and 199 mg/dL. This establishes the prevalence of those that are pre-diabetic by using the oral glucose tolerance test as the screening method.

- Impaired Fasting Glucose (mg/dL): This variable is computed by selecting cases if the value for the variable "FPG (126 md/dL)" is between 100 mg/dL and 125 mg/dL. This establishes the prevalence of those that are pre-diabetic by using the fasting plasma glucose test as the screening method.

- Higher-risk for T2DM (%): This variable is computed by selecting cases if the value for the variable "HbA1c (6.5%)" is between 5.5-6.4%. This establishes the prevalence for those that are higher-risk for T2DM, or pre-diabetic.

- OGTT: This variable is computed by selecting cases if the value for the variable "OGTT (200 mg/dL)" is greater than or equal to 200 mg/dL. This establishes the prevalence of those that are diabetic by using the oral glucose tolerance test as a screening method.

- FPG: This variable is computed by selecting cases if the value for the variable "FPG (126 md/dL)" is greater than or equal to 126 mg/dL. This establishes the prevalence for those that are diabetic by using the fasting plasma glucose screening method.

- $HbA1_c$: This variable is computed by selecting cases if the value for the variable "HbA1c (6.5%)" is greater than or equal to 6.5%. This establishes prevalence of those that are diabetic by using the $HbA1_c$ as a diabetic maintenance tool.

3.3-Statistical Methods

The Statistical Package for the Social Sciences (SPSS 19.0) PASW is the software used to run tests of agreement and concordance of screening methods for pre-diabetes and T2DM. The analysis is stratified by race/ethnicity and gender to observe differences in distributions of pre-diabetes and T2DM status by screening method. Agreements of the linear relationships of each screening method are assessed using the partial correlations function. Significance for each analysis is set at a p-value of .05, and p-values <.01 for highly significant findings.

The cross tabulations function will reveal any significant differences in screening detection of pre-diabetes and T2DM by race/ethnicity and gender, and significance of co-morbidities in the study sample. The statistical difference is provided by Pearson's chi-square. Differences in detection for males and females will be determined by the one-way analysis of variance (ANOVA). Concordance of the FPG and $HbA1_c$ against the OGTT (gold standard), will determine the following:

- Sensitivity- This is the ability for the screening test to identify patients as pre-diabetic or diabetic.

- Specificity- This is the ability for the screening test to identify patients as not pre-diabetic or diabetic.

- Positive Predictive Value- This is the number of those that test positive for pre-diabetes and diabetes that truly have the disease.

- Negative Predictive Value- This is the number of those that test negative for pre-diabetes and diabetes and truly do not have the disease.

- Overall Agreement-This value reflects the measure of equal outcomes of a screening method to OGTT (gold standard).

- Cohen's Kappa-This value expresses the level of agreement of the screening methods corrected beyond chance, where $K \leq .4$ equals weak agreement, $K \geq .5$ equals moderate agreement, and $K \geq .6$ equals strong agreement (Kleinbaum, 2008).

IV. RESULTS

4.1-Descriptive Statistics

Table 1 and Table 2 shows the frequency of clinical and non-clinical variables for men and women based on race and ethnicity. The mean age range for all respondents was 43-52 years, with Mexican Americans (MA) comprising more of the younger ages, and non-Hispanic whites (NHW) being older. Men and women of all race and ethnicities have significant differences in mean age, weight, BMI, educational attainment and income at a p-value <.01. Dyslipidemia was highest in NHW men (55%), while hypertension was highest for NHB men (47%). The measurement of blood glucose levels differed for all men, with MA men having the highest values for OGTT (127 mg/dL) and FPG (111 mg/dL). Non-Hispanic black men had the highest reading for the $HbA1_c$ test at 5.93%.

For women, mean BMI (kg/m^2) was highest in non-Hispanic black females (31.2 kg/m^2), which was significantly different from all other groups. Hypertension was also highest in non-Hispanic black females (49%), and dyslipidemia was most prevalent in non-Hispanic white females (47%). The mean blood glucose was highest for MA women using the OGTT (134 mg/dL) and FPG (112 mg/dL), but highest for NHB women for the $HbA1_c$ (5.84%).

4.2-Gylcemic Indices and Disease Prevalence

The data shows that there are significant differences in mean glycemic levels for males and females based on race and ethnicity. Table 1 and Table 2 also show that each screening method captured different proportions of disease. The OGTT captured the least amount of men classified as pre-diabetic (13-20%), where the FPG and $HbA1_c$ methods captured over 37% of cases of men that are pre-diabetic. However, the OGTT captured more diabetic cases than the other two methods (25-38%) compared to the FPG and $HbA1_c$ that captured less than 15% of

T2DM. For women, the OGTT captured the least amount of pre-diabetes for NHW, NHB and Multiracial/other groups (12-23%). This finding was not true for MA women, where all three methods detected comparable pre-diabetes with OGTT (31%), FPG (34%), and HbA1$_c$ (33%). Type 2 diabetes mellitus was best detected by OGTT for all race/ethnicities in women (39-42%), with NHB having the highest proportion of diabetics using this method. The other two methods detected less than 15% of diabetic cases.

Table 1. Distribution of characteristics of Males age 20 to 80 in the (2005-2008) National Health and Nutrition Examination Survey

	NHW	NHB	MA	Multiracial/Other	X^2	p-value
Male Sample Profile						
n=5,138	2475	1119	966	578	----	----
Age (years)	52	48	44	47	101.7	.000**
Educational Attainment	2	2	3	2	598	.000**
Income	2	2	2	2	51	.000**
Weight (kg)	89.4	90.3	82.1	81.2	125	.000**
Height (cm)	176.5	176.6	169.2	170.3	713.8	.000**
BMI (kg/m2)	28.6	28.9	28.5	27.9	48.2	.018*
SBP (mmHg)	124.4	127.4	123.1	123.3	355	0.559
DBP (mmHg)	71	73.4	70.4	72.2	338	.002**
Total Cholesterol (mg/dL)	192	189.7	201.7	200.9	42.4	.000**
HDL (mg/dL)	47.1	52.4	45.9	46.3	101.8	.000**
LDL (mg/dL)	113.2	113.1	119.3	122.8	25.6	.000**
Triglycerides (mg/dL)	146.6	130.4	153.6	148	14.1	0.055
Co-morbidities Profile						
Hypertension (%)§	41%	47%	27%	33%	109.8	.000**
Dyslipidemia (%)¥	55%	44%	48%	50%	36.3	.000*
Mean Glycemic Indices						
2-hr Oral Glucose (mg/dL)	122.7	112.7	127.5	125.5	749	0.498
Fasting Glucose (mg/dL)	106.9	108.7	111.1	108.3	501	0.213
Glycohemoglobin (%)	5.58	5.93	5.78	5.68	456	.000**
Pre-diabetes Profile by Method						
IGT: OGTT+	20%	13%	17%	19%	7.67	0.053
IFG: FPG+	41%	37%	43%	50%	8.68	.034*
High-risk: HbA1c+	38%	51%	38%	45%	19.2	.000**
T2DM Profile by Method						
Diabetic: OGTT+	37%	25%	35%	38%	12.4	.006**
Diabetic: FPG+	11%	14%	12%	7%	8	.045*
Diabetic: HbA1c+	8.7%	15%	12%	9%	71.5	.000**

p<.05*, p<.01**Data are means, unless indicated, §Hypertension if systolic/diastolic BP ≥140/90 mmHg, diagnosed with hypertension, taking medication. ¥Dyslipidemia if HDL≤35, LDL≥160 mg/dL, Total Cholesterol ≥200 mg/dL, Triglycerides ≥200 mg/dL, and taking medications for any of these conditions. +Percent of prevalence. P values were from X^2 test of means.

Table 2- Distribution of characteristics of Females age 20 to 80 in the (2005-2008) National Health and Nutrition Examination Survey

	NHW	NHB	MA	Multiracial/Other	X^2	p-value
Female Sample Profile						
n=5,428	2,495	1,199	1,050	684	----	----
Age (years)	50	47	43	46	95	.000**
Educational Attainment	2	2	2	2	560	.000**
Income	2	2	2	2	53.7	.000**
Weight (kg)	74.9	83.9	73	70.5	169.8	.000**
Height (cm)	162.7	162.7	157	157.6	625	.000**
BMI (kg/m2)	28.3	31.5	29.7	28.3	165.5	.000**
SBP (mmHg)	121.4	125.1	118.4	117.7	474	.001**
DBP (mmHg)	68.3	69.5	66.2	66.7	369	.001**
Total Cholesterol (mg/dL)	205.4	195.8	199.6	199.6	22.9	.000**
HDL (mg/dL)	59.1	61.5	54.7	56	77	.000**
LDL (mg/dL)	117.3	112.4	114.3	113	4.8	.061
Triglycerides (mg/dL)	135.8	112.3	139.1	125.8	37.2	.000**
Co-morbidities Profile						
Hypertension (%)§	38%	49%	28%	33%	122.6	.000**
Dyslipidemia (%)¥	47%	39%	38%	41%	30.2	.000**
Mean Glycemic Indices						
2-hr Oral Glucose (mg/dL)	121.7	117.1	134	121	681	.469
Fasting Glucose (mg/dL)	104	108.3	112	102.4	510	.796
Glycohemoglobin (%)	5.47	5.84	5.67	5.66	270	.000***
Pre-diabetes Profile by Method						
IGT: OGTT+	19%	12%	31%	23%	15.7	.001**
IFG: FPG+	32%	35%	34%	35%	2.2	0.532
High-risk: HbA1c+	35%	42%	33%	38%	19.2	.000**
T2DM Profile by Method						
Diabetic: OGTT+	38%	29%	42%	39%	12.4	.006**
Diabetic: FPG+	7.3%	13%	14%	7%	8	.045*
Diabetic: HbA1c+	9%	15%	11%	11%	71.5	.000**

p<.05*, p<.01**Data are means, unless indicated, §Hypertension if systolic/diastolic BP ≥140/90 mmHg, diagnosed with hypertension, taking medication. ¥Dyslipidemia if HDL≤35, LDL≥160 mg/dL, Total Cholesterol ≥200 mg/dL, Triglycerides ≥200 mg/dL, and taking medications for any of these conditions. + Percent of prevalence. P values were from X^2 test of means.

4.3- Partial Correlations and Concordance of Screening Methods by Race/Ethnicity and Gender

Partial correlations (r) are shown in Table 3 and Table 4. This analysis assesses the strength of the linear relationship of the screening method versus the health status, while controlling for age (yr) and BMI (kg/m^2). The correlation is a measure of the degree and direction of the relationship of health status and screening method, where pre-diabetes is IFG, IGT, Higher-Risk, and T2DM status is OGTT, FPG and HbA1$_c$. The results show that even after controlling for age and BMI, there are significant correlations for detecting pre-diabetes and T2DM, based on race/ethnicity and gender.

Non-Hispanic white men and women show a positive, yet weak correlation of pre-diabetes status while using the FPG method for screening (r=.12-.17). Correlation becomes negative for the FPG test and HbA1$_c$ for both NHW men and women, as the blood glucose thresholds increase. In NHB men, the correlations are all negative when comparing the FPG test with pre-diabetes and diabetes status (r≤ -.22). The same is not true for NHB women where the correlation is positive for pre-diabetes and diabetes status (r= -.27) Mexican American men and women showed positive correlations for most screening methods, as did Multiracial/Other men and women. For all men, pre-diabetes diagnosis showed significant correlation for diagnosis of diabetes in relation to the FPG test (r=.333-.440). The correlation of OGTT with T2DM diagnosis showed the most positive correlation for all men and women with the FPG and HbA1$_c$ tests (r=.554-.687).

Table 3-Partial Correlations of FPG, OGTT, and HBA1$_c$ by Race/Ethnicity: Males age 20- 80 years in the (2005-2008) National Health and Nutrition Examination Survey

NHW						
	1	2	3	4	5	6
1. IFG	1					
2. IGT	0.130**	1				
3. High-Risk	0.140**	0.146**	1			
4. OGTT	0.013**	0.644**	0.134**	1		
5. FPG	-0.288**	-0.053	0.010	0.148**	1	
6. HbA1c	-0.072	-0.182**	-0.182**	0.155**	0.333**	1

NHB						
	1	2	3	4	5	6
1. IFG	1					
2. IGT	-0.058	1				
3. High-Risk	0.291**	0.154**	1			
4. OGTT	-0.103	0.687**	0.014	1		
5. FPG	-0.220**	0.702	-0.169*	0.182*	1	
6. HbA1c	-0.174**	-0.550	-0.283**	0.243**	0.362**	1

MA						
	1	2	3	4	5	6
1. IFG	1					
2. IGT	0.142**	1				
3. High-Risk	0.202**	0.024	1			
4. OGTT	0.124	0.596**	0.01	1		
5. FPG	-0.302**	-0.053	0.041	.178**	1	
6. HbA1c	-0.121	-0.053	-0.226**	.248**	0.435**	1

Multiracial						
	1	2	3	4	5	6
1. IFG	1					
2. IGT	0.042	1				
3. High-Risk	0.209*	-0.047	1			
4. OGTT	-0.016	0.554**	-0.067	1		
5. FPG	-0.253	0.012	-0.103	0.031	1	
6. HbA1c	-0.111	-0.072	-0.123	0.132	0.440**	1

p<.05*, p<.01**IFG, IGT and High-Risk are diagnostic methods for pre-diabetes status, and OGTT, FPG and HbA1$_c$ for diabetes diagnosis. The strength of the partial correlation (r) is measured from -1 to 1.

Table 4- Partial Correlations of FPG, OGTT, and HBA1$_c$ by Race/Ethnicity: Females age 20- 80 years in the (2005-2008) National Health and Nutrition Examination

NHW	1	2	3	4	5	6
1. IFG	1					
2. IGT	0.125**	1				
3. High-Risk	0.171**	0.076	1			
4. OGTT	0.091	0.638**	0.092*	1		
5. FPG	-0.216**	-0.048	-0.076	0.118**	1	
6. HbA1c	-0.090	-0.703	-0.208**	0.129**	0.303**	1

NHB	1	2	3	4	5	6
1. IFG	1					
2. IGT	0.082	1				
3. High-Risk	0.119	0.218**	1			
4. OGTT	0.089	0.569**	0.151*	1		
5. FPG	-0.270**	-0.044	-0.098	0.189**	1	
6. HbA1c	-0.104	-0.157*	-0.355	0.069	0.478**	1

MA	1	2	3	4	5	6
1. IFG	1					
2. IGT	0.176*	1				
3. High-Risk	0.214**	0.184*	1			
4. OGTT	0.187*	0.690**	0.171*	1		
5. FPG	-0.249**	-0.129	-0.128	-0.046	1	
6. HbA1c	-0.163*	-0.116	-0.210**	0.107	0.231**	1

Multiracial	1	2	3	4	5	6
1. IFG	1					
2. IGT	0.161	1				
3. High-Risk	0.15	0.156	1			
4. OGTT	0.098	0.596**	0.237*	1		
5. FPG	-0.146	-0.089	-0.020	0.074	1	
6. HbA1c	-0.085	-0.065	-0.117	0.117	0.503**	1

p<.05*, p<.01**IFG, IGT and High-Risk are diagnostic methods for pre-diabetes status, and OGTT, FPG and HbA1$_c$ for diabetes diagnosis. The strength of the partial correlation (r) is measured from -1 to 1.

The measures of concordance are displayed in Table 5, and show the results for men and women by race/ethnicity. Sensitivity of the screening methods are low for all racial and ethnic groups, yet NHB and Multiracial/other groups are being detected as high-risk for pre-diabetes about 64% of the time using the HbA1$_c$ method versus the OGTT method. The kappa is weak (k=.135), but significant for this finding.

The prevalence for pre-diabetes was highest in NHBs and MAs, and the overall agreements for the screenings were highest in these groups. Detecting pre-diabetes in NHB was most effective using the OGTT test (86%), while the FPG and HbA1$_c$ tests were comparable in agreement for this group (75%). Positive predictive value was 72% for the HbA1$_c$ method for NHBs. Though sensitivity for detecting pre-diabetes in NHWs (55%) was highest using the HbA1$_c$ method for pre-diabetes, overall agreement was higher using OGTT to diagnose pre-diabetes. Diabetes diagnosis using the FPG method (71%) agreed more than using HbA1$_c$ (65%) for NHWs. Pre-diabetes was best detected using OGTT (82%), with HbA1$_c$ and FPG close in precision (61%) for the MA group. The results for the Multiracial/other group differ where the overall agreement for FPG (76%) is higher than HbA1$_c$ (67%).

The fasting plasma glucose detects between 44%-66% of those with T2DM, while the HbA1c method correctly detects (72%-100%) of cases for all racial and ethnic groups. Though the results are different, values of kappa are closer to zero than one. This could indicate that the concordance or discordance of the screening is most likely due to chance.

Table 5-Concordance of FPG and HbA1$_c$ against OGTT for Males and Females age 20-80 years in the (2005-2008) National Health and Nutrition Examination Survey

	Sen.	Spec.	PPV	NPV	K	OA
NHW						
IFG	52%	67%	45%	73%	.183**	62%
IGT	54%	100%	100%	79%	.602**	83.3%
High-Risk	55%	70%	51%	73%	.241**	64%
FPG	13%	96%	64%	68%	0.113	71.6%
HbA1c	6%	100%	95%	65%	0.067	65.4%
NHB						
IFG	42%	67%	32%	75%	0.08	60%
IGT	46%	100%	100%	75%	.568**	86%
High-Risk	66%	52%	33%	80	.135**	56%
FPG	18%	96%	66%	75%	.185**	75.10%
HbA1c	13%	98%	72%	75%	0.174	75.30%
MA						
IFG	53%	64%	46%	70%	.164**	60%
IGT	54%	100%	100%	78%	.588**	82.2%
High-Risk	50%	67%	49%	68%	.120**	61%
FPG	15%	95%	65%	66%	0.12	45.3
HbA1c	9.7%	100%	100%	64%	.118**	100
Multiracial						
IFG	52%	59%	47%	64%	0.116	57%
IGT	59%	100%	100%	78%	0.603**	82.7%
High-Risk	64%	65%	54%	74%	.285**	65%
FPG	5%	96%	44%	59%	0.007	76.4%
HbA1c	5%	100%	100%	62%	0.062	67%

p<.05*, p<.01**, Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Cohen's Kappa (K), Overall Agreement are all measured. K ranges from 0 to 1 to show measure of agreement.

4.4-Gender as a Risk Factor

This last analysis observes differences in glycemic indices during time of examination to see if these measures may have an impact on whether or not a respondent is pre-diabetic or diabetic. The one-way ANOVA displays diabetes status of pre-diabetic or diabetic in relation to gender. The means of the glycemic indices are compared for significance (see Table 6). The results show that there is a significant difference in glycohemoglobin (%), which is measured by the $HbA1_c$ method (p=.000), with the mean value for men being 5.7% and 5.6% for women. Pre-diabetes status was also significantly different for men and women with men more likely to have impaired fasting glucose (42%) compared to women (33%). Being tested using the $HbA1_c$ method and testing high-risk was significantly different in males (41%) from females (37%). Differences of the means for the FPG and OGTT measures were not significantly different for males and females.

Table 6- One-Way ANOVA of Glycemic Measures for Males and Females age 20 to 80 years in the (2005-2008) National Health and Nutrition Examination Survey

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	F	Sig.
						Lower Bound	Upper Bound				
Two Hour Glucose † (mg/dL)	male	1689	122.13	56.120	1.366	119.45	124.81	33	490	.180	.671
	female	1595	122.92	49.945	1.251	120.47	125.37	23	421		
	Total	3284	122.51	53.204	.928	120.69	124.33	23	490		
Fasting † Glucose (mg/dL)	male	1870	108.27	33.785	.781	106.74	109.80	45	440	2.612	.106
	female	1976	106.38	38.334	.862	104.69	108.07	38	584		
	Total	3846	107.30	36.201	.584	106.16	108.45	38	584		
Glycohemoglobin† (%)	male	4627	5.7056	1.09271	.01606	5.6741	5.7370	3.70	15.20	18.587	.000**
	female	4937	5.6130	1.00662	.01433	5.5849	5.6411	2.00	15.60		
	Total	9564	5.6578	1.05012	.01074	5.6367	5.6788	2.00	15.60		
OGTT ‡ (mg/dL)	male	1689	.3481	.47652	.01159	.3254	.3709	.00	1.00	.349	.555
	female	1595	.3580	.47956	.01201	.3344	.3815	.00	1.00		
	Total	3284	.3529	.47795	.00834	.3366	.3693	.00	1.00		
FPG ‡ (mg/dL)	male	1870	.1166	.32100	.00742	.1020	.1311	.00	1.00	.069	.792
	female	1976	.1139	.31773	.00715	.0998	.1279	.00	1.00		
	Total	3846	.1152	.31929	.00515	.1051	.1253	.00	1.00		
HbA1c ‡ (%)	male	4627	.1076	.30994	.00456	.0987	.1166	.00	1.00	3.284	.070
	female	4937	.0964	.29519	.00420	.0882	.1047	.00	1.00		
	Total	9564	.1018	.30245	.00309	.0958	.1079	.00	1.00		
Impaired Fasting Glucose[a]	male	1870	.4182	.49339	.01141	.3958	.4406	.00	1.00	34.172	.000**
	female	1976	.3274	.46939	.01056	.3067	.3481	.00	1.00		
	Total	3846	.3716	.48328	.00779	.3563	.3868	.00	1.00		
Impaired Glucose Tolerance[a]	male	1689	.1835	.38722	.00942	.1651	.2020	.00	1.00	.491	.484
	female	1595	.1931	.39486	.00989	.1737	.2125	.00	1.00		
	Total	3284	.1882	.39092	.00682	.1748	.2016	.00	1.00		
Higher Risk for T2DM[a]	male	4627	.4132	.49247	.00724	.3990	.4274	.00	1.00	20.731	.000**
	female	4937	.3678	.48226	.00686	.3544	.3813	.00	1.00		
	Total	9564	.3898	.48773	.00499	.3800	.3996	.00	1.00		

†The measurements indicate blood glucose reading at time of examination. ‡ This reading indicates T2DM status by method of screening. [a] These values indicate pre-diabetes status by screening method. Significance was derived from the ANOVA and F-statistic test of the ratio of variance within and between groups.

4.5-Research Questions

Question #1-- Is there an agreement between the fasting plasma glucose test and HbA1$_c$ and

against the oral glucose tolerance test for detecting type 2 diabetes mellitus based on

race/ethnicity and gender?

The partial correlations and concordance measures suggest that there is weak to moderate

agreement between the fasting plasma glucose test and HbA1$_c$, but this is dependent on

race and ethnicity and gender. Non-hispanic white (r=.33), NHB (r=.36), MA (r=.43),

and Multiracial/Other men (r=.44) had positive, and moderate correlations between the

FPG and HbA1$_c$ measures for detecting T2DM. For NHW (r=.30), NHB (r=.48), MA

(r=.23), and Multiracial/Other women (r=.50), the correlations were moderately

associated with each other for the FPG and HbA1$_c$ methods for detecting T2DM. The

partial correlations differed for men and women, with the partial correlation higher in

women that are NHB and Multiracial/other. These correlations show that the higher the

value of the FPG test, the higher the value for the HbA1$_c$ test.

The concordance measures of sensitivity, specifity, positive predictive value, negative

predictive value, kappa, and overall agreement were measured for FPG and HbA1$_c$

against OGTT. In terms of agreement, the OA for NHB using the FPG against OGTT

was 75% (k=.185). Mexican Americans also had perfect OA (100%) for the HbA1$_c$ test

(k=.118). Both values have low kappa measures, which indicate poor agreement, or that

agreement is the result of chance alone. These results suggest that though the FPG and

HbA1$_c$ tests are moderately correlated with each other, there are significant differences in

the diagnostic outcomes of T2DM for the different races and ethnicities.

Question #2- Is there an agreement between the fasting plasma glucose test and HbA1$_c$ and against the oral glucose tolerance test for detecting pre-diabetes mellitus based on race/ethnicity and gender?

Partial correlations for detecting pre-diabetes by screening method were significant for some groups of men and women but not others. For example, the FPG correlated with OGTT (r=.13) and HbA1$_c$ (r=.14) for NHW men and for MA men (r=.14, .20), respectively. The FPG test was not significantly correlated with OGTT for NHB or Multiracial/other men. The HbA1$_c$ method correlated significantly with OGTT for both NHW (r=.15) and NHB (r=.15) men.

The partial correlations for women showed poor correlations between FPG and OGTT for NHWs (r=.13) and MA (r=.17) women. Fasting plasma glucose correlated significantly with HbA1$_c$ for NHW (r=.17) and MA (r=.21) women. There were no significant correlations for NHB and Multiracial/other women for the FPG test. The HbA1$_c$ test correlated significantly with OGTT for MA (r=.18) and Multiracial/other women (r=.18). Overall agreement between FPG and OGTT for detecting pre-diabetes for NHW (OA=62%, k=.18) and for HbA1$_c$ (OA=64%, k=.24). Significant findings also occurred for the FPG in MA (OA=60%, k=.16). The HbA1$_c$ showed agreement with the OGTT test for NHB (OA=56%, k=.14), MA (OA=61%, k=.12) and for Multiracial/others (OA=65%, k=.28).

These results suggest that the HbA1$_c$ method may be appropriate for use in detecting potential cases of T2DM. Minority groups had significant overall agreement for the HbA1$_c$ test over the FPG test. The partial correlations for detecting pre-diabetes were

much lower, showing little no linear relationship between screening method and pre-diabetes status as the outcome.

Question #3-Are the screening methods effective in detecting pre-diabetes and type 2 diabetes mellitus for all race/ethnicities?

The distribution of disease status varied in racial and ethnic populations, and for men and women. For men and women, the fasting plasma glucose test dected less than 14% of cases compared to the oral glucose tolerance test which detected over 25%. The group of Multiracial/other men had the highest prevalence of T2DM (38%) compare the NHB men (25%). The hemoglobin $A1_c$ test found comparable cases of T2DM as the FPG with 8%-15% of cases being within the category.

The oral glucose tolerance test found 42% of Mexican American women to have T2DM, where the FPG only detected 14% of the disease in the same group. All other women were most likely to be categorized as diabetic by the OGTT method (29%-38%), over the FPG and $HbA1_c$ methods (7%-15%).

Senitivities for detecting pre-diabetes were much higher ranging in 50%-66% for all racial and ethnic groups using the $HbA1_c$ method. The FPG method showed much lower sensitivities ranging in values of 42%-53% for all groups. The $HbA1_c$ yielded more positive cases for pre-diabetes compared to the FPG.

In addition, sensitivites for detecting T2DM, were low for all groups (≤18%), but the PPV of $HbA1_c$ test versus the OGTT ranged from 75%-100%. The values were much lower for the FPG test (44%-72%) in all racial and ethnic groups. This indicates that the $HbA1_c$ could be as effective a screening method compared to the widely used FPG test for all races and ethnicities.

Question #4- Are the screening methods effective in detecting pre-diabetes and type 2 diabetes mellitus for both males and females?

Results of the one-way ANOVA showed there are differences in diagnosis of pre-diabetes between men and women. Men in this sample are more likley to test as pre-diabetic using the FPG at 42% which is 10% more than women for the category of impaired fasting glucose. Men were also more likley to be at higher-risk for T2DM using the HbA1$_c$ method at 41% compared to women at 37%. The HbA1$_c$ method is capturing similar proportions of pre-diabetes as the FPG for men and women, though women are being diagnosed less frequently. However, the HbA1$_c$ method detected the higher proportions of pre-diabetes for non-Hispanic black men (51%) and women (42%), MA women (33%), and Mutliracial other women (38%) than the FPG.

The OGTT screening method yielded the highest proportion of cases of T2DM, while both the FPG and HbA1$_c$ captured up to 30% fewer cases than OGTT for men and women. Throughout all analyses, the OGTT screening method showed the strongest correlations ($r \geq .6$), kappa ($\geq .5$), and OA ($\geq 80\%$), which is consistent with the literature.

V. DISCUSSION and CONCLUSION

5.1-Discussion

The purpose of this study was to compare the effectiveness of the fasting plasma glucose test, oral glucose tolerance test, and $HbA1_c$ for detecting pre-diabetes and type 2 diabetes mellitus in high-risk populations such as racial and ethnic minorities and women. An analysis of NHANES (2005-2008) data was performed, and showed that there were differences in rates of detection. There were also significant differences in concordance of the FPG and $HbA1_c$ tests against the OGTT (gold standard). The results show that the OGTT is still most accurate in detecting T2DM for all race/ethnicities, and for men and women (OA$\geq$80%, k$\geq$.5). The FPG and $HbA1_c$ were poorer at detecting T2DM in the study sample, yet $HbA1_c$ detected pre-diabetes at sensitivities higher than FPG for NHW (55% vs. 52%), NHB (66% vs. 42%), and Multiracial/other (64% vs. 52%). The values were almost the same for MAs (50% vs. 53%).

Though the positive predictive value for FPG was around 60% for NHW, NHB and MA groups, the value was only 44% for the Mutliracial/other group for detecting T2DM. This shows that compared to the oral glucose tolerance test (80%), there are many cases being missed in high-risk groups. The overall agreement is high for the fasting plasma glucose test in NHW and NHB, and Multiracial/other groups (75%) compared to the oral glucose tolerance test, yet kappa (.007-.185) showed low agreement. These findings are likely due to chance. This may explain why the overall agreement is low for the MA group, and high for the others. Positive predictive values are also high for the $HbA1_c$ (72-100%) in all groups. The measure of agreement for all racial and ethnic groups had a kappa of $\leq$.185, which is weak.

The one way-ANOVA was used to assess diabetes status by gender. Men of all race/ethnicities compared to women of all race/ethnicities showed significantly different means

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for testing as being pre-diabetic using the FPG (42%) and HbA1$_c$ (41%) methods. The results also show that the HbA1$_c$ method detected higher proportions of pre-diabetes for non-Hispanic black men (51%) and women (42%), MA women (33%), and Mutliracial other women (38%) than the FPG.

Screening methods were assessed for all men and women in each racial and ethnic group. Partial correlations compared health status (pre-diabetic vs. diabetic) to the screening method used to detect the condition. The OGTT is the gold standard for screening T2DM, and showed the strongest linear relationship (r>.6) for all racial and ethnic groups. HbA1$_c$ is considered the next best method (Agency for Healthcare Research and Quality, 2005), but showed weak to moderate partial correlation with the FPG in the NHB men (r=.362), MA men (r=.435) and Multiracial men (r=.440). A weak to moderate linear relationship is also seen for NHB women (r=.478) and for Multiracial/other women (r=.503) while comparing FPG. At times the results showed major significance, but when analyzed more closely; the kappa and partial correlations were mostly weak.

This study is important because it was found that the HbA1$_c$ test is comparable in precision, and is correlated with the FPG for racial and ethnic minorities. The specificities for detecting pre-diabetes using the HbA1$_c$ were higher (64-66%) for these groups than by using the standard, FPG screening method (42-49%). This study also recognizes that there are different outcomes for screening for pre-diabetes and T2DM. The same outcome has been found for other studies (American Association of Clinical Endocrinologists Board of Directors and American College of Endocrinologists Board of Trustees, 2010).

Overall, this study identifies the possibility of incorporating the HbA1$_c$ method for targeted screening for pre-diabetes in men and women that are NHB, MA, and Multiracial/Other because the measures of concordance were strong for each group (Specificity, PPV, NPV, OA). The role of gender assessed during the ANOVA showed men being at an increased risk for T2DM rather than women.

5.2- Strengths and Limitations

A major strength of this study is the use of a large, nationally diverse sample for analysis from a robust data source funded by the National Center for Health Statistics. The study also analyzes the use of HbA1$_c$ in U.S. populations while others have taken place overseas (Santos-Rey, 2010; Saukkonen, 2010; Nakagami, 2007). Some of the limitations include the inability obtain higher sensitivities to compare the screening test for the effectiveness of screening for T2DM.

Many of the cases were lost while creating sub-categories for pre-diabetes and T2DM status because not all cases fit the descriptions for recoded variables. The samples sizes were already disproportionate during the initial survey, where the size of NHB, MA, and Multiracial/other groups were less than half of the population for non-Hispanic whites. Any loss of cases could bias the results to show more than they should. For example, where the sensitivity showed perfect agreement for the HbA1$_c$ test in Multiracial other groups, there were no cases counted in the calculation. This resulted in a one-to-one ratio, and the value could have been nothing more than a missing case.

5.3-Conclusions and Recommendations

The relationship of race/ethnicity and gender were considered while comparing the effectiveness of screening tests for pre-diabetes and T2DM. The ability for the OGTT, FPG and HbA1$_c$ to screen effectively for minorities has been disputed in the literature (Ariza, 2010; Borai, 2011; Colagiuri, 2011). This study is important because this study provides additional information for better detection of pre-diabetes and T2DM for racial and ethnic minorities, who bear a higher burden of T2DM (National Center for Chronic Disease Prevention and Health Promotion, 2011). Prevention is essential for reversing or delaying pre-diabetes and T2DM, and HbA1$_c$ could be added as a standard method of detection. However, the current concern is that the HbA1$_c$ method will misdiagnose racial and ethnic minorities (Borai, 2011; Carnethon, 2002; Esakoff, 2005 ; Olson, 2010).

One recommendation is for further research of more survey years from NHANES to help assess the effectiveness of screenings, which will include more data points. This can validate this and other studies about screening to better inform clinicians about their options (Bisht, 2011). More academic research will aid in improving policy for screening. Updated health policy can include the HbA1$_c$ as a standard precursor to the FPG or OGTT during initial screening for pre-diabetes or T2DM, because it is the most stable testing method (Borai, 2011). While there is evidence supporting focused screening for those that have hypertension and dyslipidemia (U.S. Preventive Services Task Force, 2008, American Diabetes Association, 2010), the USPSTF recommends more studies to be done to support focused screening for other risk factors (2008).

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