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# Diagnostic performance of glycated hemoglobin for diabetic retinopathy in non-diabetic older overweight/obese African-Americans

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ABSTRACT

*Objectives:* Although clinicians do not routinely screen for diabetic retinopathy in non-diabetic patients, previous studies have shown that diabetic retinopathy can occur in patients with prediabetes. However, due to the limitations of glycated hemoglobin (HbA1c) in overweight/obese subjects, African-Americans and older adults, little is known about the correlation between HbA1c and diabetic retinopathy in non-diabetic older overweight/obese African-Americans. The aims of this study were to determine the association between HbA1c and diabetic retinopathy, and the optimal diagnostic threshold of HbA1c that predicts diabetic retinopathy in non-diabetic older overweight/obese African-Americans.

*Methods:* The 2005–2012 data from the U.S. National Health and Nutrition Examination Surveys (NHANES) were utilized for this study. Prevalence odds ratios from logistic regression analyses were used to estimate risks of diabetic retinopathy across HbA1c categories, adjusting for age, sex, and hypertension. Receiver operating characteristic curve was used to determine diagnostic cutoff point of HbA1c for prevalent diabetic retinopathy.

*Results:* There were gradients of increasing prevalence and odds of diabetic retinopathy with increasing HbA1c in non-diabetic overweight/obese African-Americans 50 years of age and older. HbA1c cut-off point of 5.2% (AUC = .726, 95% CI = 0.696–0.756) was found to maximize sensitivity [93.5%; 95% CI: 83.2–95.7] for diabetic retinopathy, though specificity [22.1%; 95% CI 19.9–32.8] was low.

*Conclusion:* Current criteria for diagnosis of prediabetes are effective in identifying many older overweight/obese African Americans with diabetic retinopathy. Based on our analysis, a lower HbA1c of 5.2% could serve as a more sensitive cutoff point for defining prediabetes in this population subgroup.



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## 1. Introduction

The search for an optimal testing strategy to identify the greatest number of patients with abnormal blood glucose levels has been the subject of many epidemiological and clinical studies [1–4]. From a population-level perspective, it is imperative for a screening test to be highly sensitive so that it can identify as many people as possible with a specific disease. For patients with type 2 diabetes, it is essential to diagnose patients accurately in order to prevent macro- and microvascular complications such as cardiovascular disease, diabetic nephropathy, and diabetic retinopathy. For patients who have impaired glucose metabolism or "prediabetes," clinicians can intervene with lifestyle modifications that may be able to prevent the development of overt diabetes. Prediabetes is a state of dysglycemia in which blood glucose values are higher than normal, but not high enough to be classified as diabetes. It is essential that clinicians and epidemiologists have a sensitive and specific diagnostic test to identify individuals with prediabetes.

Until recently, fasting plasma glucose (FPG) and oral glucose tolerance testing (OGTT) were the two most widespread tests for prediabetes and diabetes. FPG is a rapid, minimally invasive, and reproducible screening and diagnostic test. While OGTT is the gold standard for diagnosing diabetes, the test is laborious, requiring several hours to complete, and can be uncomfortable for patients. In recent years, the American Diabetes Association (ADA) has recommended the use of hemoglobin A1C (HbA1c) testing to identify subjects with abnormal blood glucose [5]. The HbA1c provides an estimation of the average blood glucose level over the previous 60–90 days, and can thus serve as a benchmark for retrospective analysis of glucose control [5]. Some advantages of the HbA1c over OGTT include its quickness and convenience – it does not require the patient to be fasting. Like fasting or random plasma glucose testing, the HbA1c test can be done in a lab or point-of-care setting.

Currently, the ADA defines diabetes as an HbA1c of 6.5% or greater, which corresponds to an average blood glucose level of 150 mg/dL [6]. As HbA1c rises, reflecting worsening blood glucose control, the risk for complications of diabetes increases. However, it is not as well known if patients with HbA1c values below 6.5% are at risk for macro- and microvascular complications of diabetes, and if so, at what HbA1c level the risk begins to increase. While the cutoff values of available tests for diabetes are well defined, where prediabetes begins remains a subject of debate. Current recommendations define prediabetes as an HbA1c of 5.7–6.4% [6–8] for all patients, but others have advocated using different values for prediabetes and diabetes based on ethnicity or race [9–11]. Previous epidemiological evidence suggests that African-Americans have higher HbA1c values at the same blood glucose level than Caucasians do [12,13], and the HbA1c is less accurate in reflecting blood glucose levels in patients at older ages [14] with higher body mass index (BMI) and with anemia [15].

The current HbA1c diagnostic criteria were defined using large epidemiologic data based on thresholds for diabetic retinopathy [1,2]. Diabetic retinopathy is one of the earliest complications of diabetes [15,16], and can be one of the most devastating. HbA1c is highly correlated with diabetic retinopathy in known diabetics [17,18]. Previous studies have shown that diabetic retinopathy can occur even in patients with prediabetes [19,20], however, clinicians do not routinely screen this population for diabetic retinopathy. In this study, we set out to determine if there is an association between HbA1c and diabetic retinopathy in non-diabetic older overweight/obese African-Americans. We also sought to determine the optimal diagnostic threshold of HbA1c that puts non-diabetic older overweight/obese African-Americans at risk for diabetic retinopathy. Older overweight/obese African-Americans are at much greater risk for diabetes compared to young non-obese and other racial/ethnic peers [21]. Knowing the association between HbA1c and medical complications like diabetic retinopathy will provide further insight into what HbA1c value make patients as individuals with prediabetes.

## 2. Subjects, materials and methods

### 2.1. Subjects and study design

The 2005–2012 data from the U.S. National Health and Nutrition Examination Surveys (NHANES) were utilized for this study. NHANES, a longitudinal survey with associated physical exam and laboratory components, is a publicly available dataset from the United States Centers for Health Statistics [22]. It is administered to a representative sample of U.S. non-institutionalized civilians. In the surveys, study participants were interviewed in their homes, while laboratory and physical examinations were performed in mobile centers for a limited number of participants. Full details about NHANES methodology are available elsewhere [23,24].

### 2.2. Inclusion and exclusion criteria

For this study, we included non-Hispanic African-American participants over 50 years old who had a BMI of 25 kg/m$^2$ or higher. If there were missing values for age, weight, or height, participants were excluded. Participants who had diabetes by FPG or OGTT [(FPG ($\geqslant$125 mg/dl), OGTT ($\geqslant$200 mg/dl)], as well as past or current users of anti-diabetic medication were excluded from this analysis. Participants with missing values for sex, HbA1c, and blood pressure were excluded, as were those with a positive family history of diabetes. In terms of age, gender, weight, height and BMI participants who were eligible in this study were not different from those who were excluded due to missing data.

### 2.3. Definition of terms

#### 2.3.1. Diabetic retinopathy

As part of the NHANES questionnaires, participants were asked: *Has a doctor ever told you that diabetes has affected your eyes or that you had retinopathy?* In 2005–2008, retinal imaging exams were also performed on eligible NHANES participants using digital retinal photography to assess the presence of retinal diseases. Digital images from the exams were evalu-