A1C Combined With Glycated Albumin Improves Detection of Prediabetes in Africans: The Africans in America Study

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OBJECTIVE

Slowing the diabetes epidemic in Africa requires improved detection of prediabetes. A1C, a form of glycated hemoglobin A, is recommended for diagnosing prediabetes. The glycated proteins, fructosamine and glycated albumin (GA), are hemoglobin-independent alternatives to A1C, but their efficacy in Africans is unknown. Our goals were to determine the ability of A1C, fructosamine, and GA to detect prediabetes in U.S.-based Africans and the value of combining A1C with either fructosamine or GA.

RESEARCH DESIGN AND METHODS

Oral glucose tolerance tests (OGTT) were performed in 217 self-identified healthy African immigrants (69% male, age 39 ± 10 years [mean ± SD], BMI 27.6 ± 4.5 kg/m^2). A1C, fructosamine, and GA were measured. Prediabetes was diagnosed by American Diabetes Association criteria for glucose obtained from a 2-h OGTT. The thresholds to diagnose prediabetes by A1C, fructosamine, and GA were the cutoff at the upper tertile for each variable: ≥5.7% (39 mmol/mol) (range 4.2–6.6% [22.4–48.6 mmol/mol]), ≥230 μmol/L (range 161–269 μmol/L), and ≥13.35% (range 10.20–16.07%), respectively.

RESULTS

Prediabetes occurred in 34% (74 of 217). The diagnostic sensitivities of A1C, fructosamine, and GA were 50%, 41%, and 42%, respectively. The *P* values for comparison with A1C were both >0.3. Combining A1C with either fructosamine or GA increased sensitivities. However, the sensitivity of A1C combined with fructosamine was not better than for A1C alone (72% vs. 50%, *P* = 0.172). In contrast, the sensitivity of A1C combined with GA was higher than for A1C alone (78% vs. 50%, *P* < 0.001).

CONCLUSIONS

As individual tests, A1C, fructosamine, and GA detected ≤50% of Africans with prediabetes. However, combining A1C with GA made it possible to identify nearly 80% of Africans with prediabetes.

Diabetes is a global epidemic that has begun to seriously affect low- and middle-income countries (1). By 2035, the International Diabetes Federation (IDF) predicts that 66 million sub-Saharan Africans will have prediabetes and 42 million will have diabetes (1). This represents a 20-year change in prevalence of 109% and is the highest anticipated increase in the world (1).

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The transition from prediabetes to diabetes can be delayed or prevented by identifying people with prediabetes and intervening with lifestyle modifications (2–7). In contrast, interventions with lifestyle modifications in cohorts with established diabetes have revealed no decrease in all-cause mortality, cardiovascular events, or microvascular complications (6). Therefore, an enhanced focus on prediabetes may be an important way forward. The first step is to identify screening programs for prediabetes that are effective in Africans.

At this time, screening for prediabetes in Africa is underfunded and insufficiently studied. Africa has the highest prevalence of people with undiagnosed hyperglycemia in the world (1). The degree to which this high prevalence is due to inadequately performing screening tests rather than lack of access to care needs to be addressed (8). In short, a rigorous evaluation of the ability of screening tests to detect prediabetes in Africans needs to be undertaken because the scarce funding available must be invested in effective tests.

A1C is a form of glycated hemoglobin A. With the standardization of the A1C assay, A1C has been recommended for the diagnosis of prediabetes (9,10). However, with oral glucose tolerance test (OGTT) as the reference method, A1C has a diagnostic sensitivity of less than 60% (11–13). Furthermore, A1C cannot be measured in the absence of hemoglobin A. Therefore, A1C cannot be used in homozygous hemoglobinopathies common in Africa, such as sickle cell anemia, or compound heterozygotes such as hemoglobin SC disease (14,15).

The glycated proteins, fructosamine and glycated albumin (GA), have been proposed as hemoglobin-independent alternatives to A1C (16–19). Fructosamine is a measure of all glycated proteins in plasma. GA is a subfraction of fructosamine. Similar to A1C, blood for analyses of fructosamine and GA levels can be obtained any time of day without regard to recent food intake. However, fructosamine and GA have never been evaluated as diagnostic tests in Africans. With the OGTT as our diagnostic standard, our goals were to determine the ability of A1C, fructosamine, and GA to detect prediabetes in U.S.-based Africans and whether there would be added diagnostic value in combining A1C with fructosamine or GA.

RESEARCH DESIGN AND METHODS

A total of 222 African immigrants in the Africans in America cohort were evaluated. The Africans in America cohort was established to determine the cardiometabolic health status of African immigrants (13,20–22). At the initial telephone interview, all participants had to self-identify as healthy and specifically deny a history of diabetes. After enrollment, one immigrant was excluded because he was found to have hereditary persistent fetal hemoglobin. This condition makes determination of A1C by high-performance liquid chromatography (HPLC) problematic (23). After the OGTT, an additional four immigrants were excluded because they were found to have previously undiagnosed, asymptomatic diabetes (Fig. 1). The characteristics of these four individuals are provided in Supplementary Table 1*A*.

The population under analysis therefore consisted of 217 individuals (69% male) aged 39 ± 10 years (mean ± SD; range 20–64) and with a BMI of 27.6 ± 4.5 kg/m^2 (range 18.2–41.2). At the time of participation, enrollees lived in the metropolitan Washington, DC, area, self-identified as black Africans born in equatorial Africa, and reported that both of their parents were black Africans born in equatorial Africa. The participants' regions of origin in Africa were West (55%), Central (21%), and East (24%). As described previously, recruitment was achieved by newspaper advertisements, flyers, and the National Institutes of Health (NIH) Web site (13,20,22). The study was approved by the National Institute of Diabetes and Digestive and Kidney Diseases Institutional Review Board. All enrollees gave informed written consent.

Two outpatient visits were held at the NIH Clinical Center in Bethesda, MD. At visit 1, a medical history, physical examination, and electrocardiogram were performed. Routine blood tests were done to document the absence of anemia as well as kidney, liver, and thyroid disease.

For visit 2, participants fasted for 12 h and came to the Clinical Center at 7 A.M. for an OGTT. Baseline blood samples were obtained for fasting plasma glucose (FPG), insulin, A1C, fructosamine, GA, and hemoglobin electrophoresis. An OGTT was performed with 75 g dextrose (Trutol 75; Custom Laboratories, Baltimore, MD). Glucose and insulin levels were obtained at 30, 60, and 120 min. Waist circumference (WC) was measured at the level of the anterior iliac crest, and the mean of three WC determinations was reported. Visceral adipose tissue (VAT) was measured at the level of L2-3 by abdominal computed tomography (CT) scans (20).

Diagnosis of Diabetes, Prediabetes, and Normal Glucose Tolerance

Diabetes was diagnosed according to American Diabetes Association (ADA)

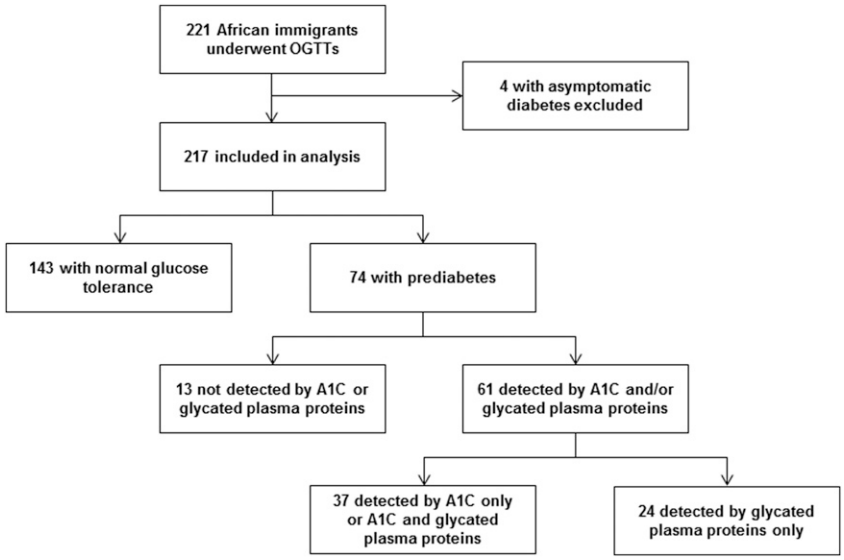

Figure 1—Design of the Africans in America study evaluating the ability of A1C, fructosamine, and GA to detect prediabetes.

criteria for asymptomatic diabetes; therefore, the presence of at least two of the three criteria listed below were required:

- FPG ≥7 mmol/L
- 2-h glucose ≥11.1 mmol/L
- A1C ≥6.5% (≥48 mmol/mol) (24)

Prediabetes was defined as FPG ≥5.6 mmol/L and <7 mmol/L and/or 2-h glucose ≥7.8 mmol/L and <11.1 mmol/L (24). If the 2-h glucose was >11.1 mmol/L but a second criterion for diabetes was not present, the category of prediabetes was assigned.

Normal glucose tolerance was defined as FPG <5.6 mmol/L and 2-h glucose <7.8 mmol/L (24).

A1C, fructosamine, and GA were evaluated according to their ability to distinguish between individuals with prediabetes and normal glucose tolerance. Unlike A1C, there are no established diagnostic thresholds for fructosamine and GA (18); therefore, we followed a procedure similar to the Atherosclerosis Risk in Communities (ARIC) study (18). First, A1C (range 22.4–48.6 mmol/mol) was divided into tertiles and quartiles. We found that the A1C cutoff was 5.7% (39 mmol/mol) for the upper tertile and 5.8% (40 mmol/mol) for the upper quartile. The former corresponds to the ADA threshold for prediabetes (24). Therefore, fructosamine (range 161–269 μmol/L) and GA (range 10.20–16.07%) were divided into tertiles. The upper tertile cutoffs were ≥230 μmol/L for fructosamine and ≥13.35% for GA. These thresholds were used to determine the diagnostic sensitivity of fructosamine and GA in detecting prediabetes.

Analytic Measures

Hemoglobin, hematocrit, and mean corpuscular volume were measured in EDTA-anticoagulated whole blood using a Sysmex XE-5000 analyzer (Chicago, IL). Glucose, total bilirubin, direct bilirubin, liver enzymes, blood urea nitrogen, and creatinine were measured in serum using the Roche Cobas 6000 analyzer (Roche Diagnostics, Indianapolis, IN). Insulin was measured in serum on the Cobas 6000 instrument. Iron, transferrin, and ferritin levels were available in 149 consecutively enrolled participants and were analyzed in serum on the Immulite XP analyzer (Siemens Healthcare, Malvern, PA).

Fructosamine was measured in plasma on the Cobas 6000 using a colorimetric nitroblue tetrazolium assay. The interassay coefficient of variation was 2.9% at 308 μmol/L and 2.6% at 521 μmol/L. GA was measured in plasma on the Cobas 6000 using the Lucica GA-L enzymatic assay provided by Asahi Kasei Pharma (Tokyo, Japan). The interassay coefficient of variation for GA was 1.7% at 0.58 g/L and 4.8% at 1.67 g/L. Total albumin was measured with bromocresol purple. GA was expressed as a percentage of total albumin.

A1C by HPLC

A1C values and hemoglobin phenotype (e.g., AA, AS, AC, AE, AF) were determined by HPLC using two different National Glycohemoglobin Standardization Program–certified instruments made by the same manufacturer using the same HPLC technology (Bio-Rad Laboratories, Hercules, CA). A1C samples from the first 138 consecutively enrolled participants were measured on the Bio-Rad Variant II instrument. A1C measurements for the next 79 consecutively enrolled participants were performed on a D10 instrument. The correlation (R^2) between the Bio-Rad II and D10 instruments was 0.9934 (13). The mean bias between the Bio-Rad Variant II and D10 instruments was 0.07 (1.21%).

Hemoglobin Electrophoresis

To verify the hemoglobin phenotype reported by HPLC, hemoglobin electrophoresis was performed in 133 participants, 130 of whom were consecutively enrolled and 3 in whom hemoglobin electrophoresis was identified by NIH record review. Hemoglobin electrophoresis was performed in cellulose acetate (pH 8.4–8.6) and citrate agar (pH 6.0–6.3) using a Helena Zip Zone electrophoresis instrument (Helena Laboratories, Beaumont, TX). Identities of hemoglobin proteins were confirmed by comparison with known samples of hemoglobin A, S, C, E, and F. In the 133 participants who had both hemoglobin electrophoresis and HPLC, hemoglobin electrophoresis confirmed the hemoglobin phenotype reported by HPLC.

Statistics

Unless otherwise stated, data are presented as mean ± SD. Group comparisons were made using unpaired *t* tests, one-way analyses of variance, and the χ^2 test as appropriate. Linear relationships between variables were explored using the Pearson correlation coefficient. *P* values ≤0.05 were considered significant.

Insulin resistance was determined by the Matsuda index $\left(\frac{10,000}{\sqrt{fasting\ insulin \times fasting\ glucose \times mean\ glucose \times mean\ insulin}}\right)$ (25). Mean glucose was the average of glucose levels from the OGTT obtained at fasting and 30, 60, and 120 min. Mean insulin was the average of insulin levels obtained at the same time points. β-Cell secretion was assessed with the insulinogenic index $\left(\frac{30\ min\ insulin - fasting\ insulin}{30\ min\ glucose - fasting\ glucose}\right)$ (26). Adequacy of β-cell function was determined with the oral disposition index $\left(\frac{insulinogenic\ index}{fasting\ insulin}\right)$ (26).

The McNemar test for matched pairs was used to compare the sensitivity of A1C to fructosamine and A1C to GA. In addition, receiver operating characteristic curves were used to compare the ability of A1C, fructosamine, and GA to predict the presence of prediabetes. Logistic regression was used to compare the combination of A1C and fructosamine to A1C and the combination of A1C and GA to A1C. Analyses were performed with STATA 14.0 software (StataCorp LP, College Station, TX).

RESULTS

According to the glucose criteria for the OGTT, the overall prevalence of prediabetes was 34% (74 of 217). The prevalence of prediabetes in participants from West, Central, and East Africa was 29% (34 of 118), 43% (20 of 46), and 38% (20 of 53), respectively (*P* = 0.17). In addition, there was no variation by African region of origin in sex, age, body fat distribution, or social factors, such as marital status, income, health insurance, or education (Supplementary Table 2).

Furthermore, markers of glucose metabolism, such as fasting glucose and 2-h glucose, Matsuda index, insulinogenic index, and oral disposition index, were similar across African regions (Supplementary Table 2). The one major difference by African region of origin occurred in the category of variant hemoglobin (Supplementary Table 2). West and Central Africans were more likely than East Africans to have hemoglobin S or C

trait. In addition, mean corpuscular volume was lowest in West Africans (Supplementary Table 2).

Because the focus of this investigation was on the ability of A1C, fructosamine, and GA to identify prediabetes and the prevalence of prediabetes did not vary by African region, the decision was made to examine the cohort as a single group.

As stated above, the prevalence of prediabetes was 34% (74 of 217). The 74 individuals with prediabetes were older and had a higher BMI, higher WC, and more VAT than the 143 individuals with normal glucose tolerance (Table 1). Fasting and 2-h glucose were higher in the group with prediabetes (Table 1). In addition, the degree of insulin resistance measured by the Matsuda index and β-cell function measured by the oral disposition index were worse in the group with prediabetes (Table 1). However, hemoglobin, hematocrit, frequency of variant hemoglobin, iron status, albumin, creatinine, and estimated glomerular filtration rate did not differ by glucose tolerance category (Table 1).

Prediabetes Glucose Pattern Based on the OGTT

Four different glucose patterns were observed in the 74 individuals with prediabetes:

1. 12% (9 of 74)— impaired FPG only
2. 57% (42 of 74)—2-h glucose ≥7.8 mmol/L and <11.1 mmol/L (impaired glucose tolerance)
3. 16% (12 of 74)—impaired FPG and impaired glucose tolerance
4. 15% (11 of 74)—2-h glucose ≥ 11.1 mmol/L but FPG <7 mmol/L and A1C <6.5% (<48 mmol/mol)

The characteristics of the 11 individuals in category 4 are provided in Supplementary Table 1*B*.

Characteristics of the Individuals With Prediabetes

Thirteen of the 74 individuals discovered by the OGTT to have prediabetes were not identified by A1C, fructosamine, or GA (Fig. 1). The 61 individuals with prediabetes detected by A1C, fructosamine, or GA were divided into two groups: those detected by A1C only or A1C and either fructosamine or GA, and those detected by fructosamine or GA (Fig. 1 and Table 2). As anticipated, the group detected by A1C had higher A1C levels. The group detected by glycated plasma proteins only, meaning either fructosamine or GA but not A1C, had higher fructosamine and GA levels (Table 2). The two groups did not differ in any measure of glucose tolerance, including FPG, 2-h glucose, Matsuda index, insulinogenic index, or the oral disposition index (Table 2). In addition, the two groups did not differ in frequency of variant hemoglobin or albumin levels (Table 2). Yet, there were clear differences by group in age, BMI, WC, and VAT (Table 2). Immigrants whose prediabetes was detected by glycated plasma proteins only were younger and had lower BMI, smaller WC, and less VAT than individuals identified by A1C (Table 2).

Table 1—Participant characteristics by glucose tolerance status*

Parameter	Total (*N* = 217)	Normal (*n* = 143 [66%])	Prediabetes (*n* = 74 [34%])	*P* value†
Age (years)	39 ± 10	36 ± 10	43 ± 10	<0.01
BMI (kg/m^2)	27.6 ± 4.5	27.0 ± 4.5	28.6 ± 4.3	0.01
WC (cm)	90 ± 12	88 ± 11	95 ± 11	<0.01
VAT (cm^3) (*n* = 210)	102 ± 76	80 ± 64	143 ± 80	<0.01
Fasting glucose (mmol/L)	5.0 ± 0.5	4.8 ± 0.3	5.3 ± 0.6	<0.01
2-h glucose (mmol/L)	7.2 ± 2.0	6.2 ± 0.9	9.3 ± 1.9	<0.01
Matsuda index	7.00 ± 4.52	7.86 ± 4.72	5.35 ± 3.61	0.01
Insulinogenic index	2.42 ± 8.51	3.08 ± 10.44	1.15 ± 0.79	0.11
Oral disposition index	0.39 ± 0.90	0.50 ± 1.10	0.18 ± 0.10	0.01
Hemoglobin (g/L)	141 ± 13	139 ± 14	143 ± 12	0.08
Hematocrit (%)	41.9 ± 3.5	41.7 ± 3.6	42.4 ± 3.1	0.20
Variant hemoglobin, % (*n*/*N*)	20 (44/217)	18 (25/143)	26 (19/74)	0.16
Iron (μmol/L) (*n* = 149)	15.2 ± 5.0	15.6 ± 5.0	14.7 ± 4.8	0.26
Transferrin (g/L) (*n* = 149)	2.46 ± 0.37	2.44 ± 0.37	2.49 ± 0.37	0.44
Saturation (%) (*n* = 149)	25 ± 9	26 ± 9	24 ± 9	0.14
Ferritin (pmol/L) (*n* = 149)	267 ± 216	245 ± 211	295 ± 222	0.17
Albumin (g/L)	40 ± 3	40 ± 3	40 ± 3	0.70
Creatinine (μmol/L)	80 ± 17	79 ± 15	82 ± 20	0.16
eGFR (mL/min/1.73 m^2)‡	109 ± 20	109 ± 18	108 ± 23	0.86

Unless noted otherwise, results are available for all 218 participants and are presented as mean ± SD. eGFR, estimated glomerular filtration rate. *Glucose tolerance status based on glucose criteria for the OGTT. †Comparisons were by unpaired *t* tests for continuous variables and by χ^2 for categorical variables. ‡Based on the MDRD Study Equation.

Sensitivity and Specificity Using Glucose Criteria From the OGTT

As individual tests, the diagnostic sensitivities of A1C, fructosamine, and GA were 50%, 41%, and 42%, respectively (Table 3) (both *P* values for comparison with A1C% >0.3). The corresponding specificities for A1C, fructosamine, and GA were 75%, 66%, and 71%, respectively. Similarly, the areas under the receiver operating characteristic curves (95% CI) for the identification of prediabetes by A1C, fructosamine, and GA were 0.63 (0.55, 0.71), 0.55 (0.47, 0.63), and 0.58 (0.50, 0.66), respectively (*P* = 0.36) (Supplementary Fig. 1).

A1C Combined With Either Fructosamine or GA

Combining A1C with either fructosamine or GA increased the diagnostic sensitivities to 72% and 78%, respectively. However, the combination of A1C and fructosamine was not significantly better than for A1C alone (*P* = 0.172). In contrast, the combination of A1C and GA was significantly better than A1C alone (*P* < 0.001) (Table 3).

Relationship Between Body Size Measures and Glycemic Markers

There was a positive correlation between BMI and A1C (*r* = 0.23, *P* = 0.001). Yet, the correlation was negative between BMI and fructosamine (*r* = −0.29, *P* < 0.001) and between BMI and GA (*r* = −0.25, *P* < 0.001) (Supplementary Fig. 2). The correlation between VAT and A1C was positive (*r* = 0.27, *P* < 0.001). In contrast, the correlations were negative between VAT and fructosamine (*r* = −0.18, *P* = 0.009) and VAT and GA (*r* = −0.21, *P* = 0.002) (Supplementary Fig. 2).

CONCLUSIONS

Because intervention at the prediabetic stage prevents or delays the onset of

Table 2—Characteristics of African immigrants with prediabetes detected by A1C versus detected only by glycated proteins

Characteristic	Detected by A1C* (n = 37)	Detected by glycated plasma proteins only (n = 24)	P value†
A1C (%)	6.0 ± 0.3	5.2 ± 0.4	<0.01
A1C (mmol/mol)	42 ± 3	33 ± 4	
Fructosamine (μmol/L)	225 ± 14	235 ± 12	<0.01
GA (%)	12.8 ± 1.2	14.1 ± 0.8	<0.01
Fasting glucose (mmol/L)	5.4 ± 0.6	5.3 ± 0.6	0.35
2-h glucose (mmol/L)	9.2 ± 2.1	9.4 ± 1.9	0.74
Matsuda index	5.54 ± 4.14	5.40 ± 3.26	0.89
Insulinogenic index	1.02 ± 0.59	1.30 ± 1.09	0.20
Oral disposition index	0.16 ± 0.11	0.19 ± 0.10	0.31
Variant hemoglobin (%)	30%	25%	0.69
Albumin (g/L)	39 ± 3	40 ± 2	0.20
Age (years)	46 ± 9	39 ± 8	<0.01
BMI (kg/m^2)	30.3 ± 4.6	26.6 ± 3.6	<0.01
WC (cm^2)	99 ± 11	90 ± 11	<0.01
VAT (cm^3)	167 ± 76	112 ± 80	<0.01

Data are presented as mean ± SD or as indicated. *Detected by A1C only or by A1C and glycated plasma proteins. †Comparisons were by unpaired t tests for continuous variables and by χ^2 for categorical variables.

diabetes, we focused on evaluating ways to improve the detection of prediabetes in Africans. We found in African immigrants that the maximum rate of detection of prediabetes when A1C, fructosamine, or GA were used as single tests was ≤50%. Therefore, as individual screening tests, A1C, fructosamine, and GA are unable to detect the majority of Africans with prediabetes. However, we speculated that diagnostic sensitivity might improve if A1C, a hemoglobin-dependent test, was combined with a hemoglobin-independent alternative such as fructosamine or GA. Sensitivity for the combined tests increased from 50% for A1C alone to 72% for the combination of fructosamine and A1C and to 78% for GA and A1C. But it was only for the latter that the increase in sensitivity over A1C alone was significant ($P < 0.001$).

To understand why the combination of A1C and GA had a higher sensitivity than A1C alone but the combination of A1C and fructosamine did not have a statistically significant higher sensitivity than A1C alone, we turn our attention to the 24 people whose prediabetes was detected by glycated plasma proteins only: 13 were detected by both tests, 8 by GA only, and 3 by fructosamine only.

Table 3—Sensitivities and specificities for the prediction of prediabetes

Parameters	Sensitivity % (95% CI)	Specificity % (95% CI)	
A1C (≥5.7%)	50 (39, 61)	75 (67, 81)	
Fructosamine* (≥230 μmol/L)	41 (29, 52)	66 (58, 74)	
GA† (≥13.35%)	42 (31, 54)	71 (62, 78)	
A1C + fructosamine‡	72 (61, 81)	52 (40, 63)	For the 53 people detected: 23 identified by A1C only 16 by fructosamine only 14 by A1C and fructosamine
A1C + GA§	78 (67, 87)	55 (44, 60)	For the 58 people detected: 27 identified by A1C only 21 by GA only 10 by A1C and GA

*Comparison of A1C vs. fructosamine, P = 0.34. †Comparison of A1C vs. GA, P = 0.47. ‡Comparison of A1C + fructosamine vs. A1C, P = 0.172. §Comparison of A1C + GA vs. A1C, $P < 0.001$.

In short, fructosamine detected fewer people with prediabetes than GA. There have been previous reports which suggest that GA is a superior diagnostic test than fructosamine (16,19,27). We now extend this finding to African immigrants.

Next, we wanted to determine whether there were demographic or metabolic differences in the group with prediabetes detected by A1C (n = 37) compared with the group whose prediabetes was detected by a glycated plasma protein only (n = 24). Interestingly, glucose tolerance status, including degree of insulin resistance and β-cell function, were similar in the group detected by A1C and in the group detected by glycated proteins. But, the group with prediabetes detected by glycated plasma proteins only was younger, with a lower BMI, smaller WC, and less VAT than the group detected by A1C. This result is consistent with reports from East Asia (17,28–31).

Working with three different Japanese cohorts, Koga et al. (28,29,32) reported a positive correlation between A1C and BMI but a negative correlation between BMI and GA. Ikezaki et al. (17) also reported a negative correlation between BMI and GA. Examining a Chinese cohort, Wang et al. (31) found an inverse relationship between BMI and GA as well as between VAT and GA. On the basis of these reports from Japan and China and our observation that the glycated plasma proteins did a better job than A1C in identifying the less obese African immigrants with prediabetes, we examined the relationship between BMI, VAT, and A1C and both fructosamine and GA. All of the correlations we performed mirrored the results previously reported in East Asian populations (Supplementary Fig. 2). Our investigation therefore extends the findings made in East Asians to another racial group.

There is important clinical relevance to the observation of an inverse relationship between BMI and GA. Ikezaki et al. (17) have theorized that this inverse relationship means that GA will enhance the detection of prediabetes in the nonobese. Our data in African immigrants is consistent with this view. Work remains to be done to determine why glycated plasma proteins are inversely related to body size. The leading hypothesis is that chronic inflammation associated with obesity leads to rapid turnover of albumin (28,29,32).

Determination of Glucose Tolerance Status

To evaluate the diagnostic efficacy of A1C, fructosamine, and GA, glucose criteria from the OGTT was the diagnostic standard. The OGTT has been used by all of the major lifestyle intervention trials to diagnose prediabetes and to document progression to diabetes (3–5). In addition, the OGTT was used as the gold standard to evaluate the diagnostic efficacy of GA in Asian populations (17,19).

The challenge in this study was categorizing the 11 of 74 individuals who had 2-h glucose ≥11.1 mmol/L but fasting glucose <7 mmol/L and A1C <6.5% (<48 mmol/mol) (Supplementary Table 1). In asymptomatic individuals, the ADA recommends the presence of two tests consistent with the diagnosis of diabetes before the diagnosis of diabetes is made. The four individuals we diagnosed with asymptomatic diabetes had elevated values for all five parameters we looked at: A1C, fasting glucose, 2-h glucose, fructosamine, and GA (Supplementary Table 1). Therefore these four individuals would have come to medical attention independent of which diagnostic test was used.

In contrast, the 11 people with 2-h glucose ≥11.1 mmol/L only have a very high chance of escaping early detection. For example, 5 of the 11 with 2-h glucose ≥11.1 mmol/L had A1C levels <5.7% and 4 had FPG <5.6 mmol/L. Because repeat testing was not done, a clear diagnosis of diabetes could not be confirmed, and these individuals were considered in this study to have prediabetes. Regardless of whether these individuals have prediabetes or diabetes, it is essential to provide follow-up testing.

In addition, the group with asymptomatic diabetes (n = 4) and the group with isolated elevated 2-h glucose (n = 11) were distinctly different from each other. By Mann-Whitney, all five variables, A1C, fasting glucose, 2-h glucose, fructosamine, and GA, were significantly higher in the asymptomatic diabetes group (n = 4) than the isolated elevated 2-h glucose group (n = 11) (Supplementary Table 1).

Finally, when we excluded the isolated elevated 2-h glucose group (n = 11) and repeated all of the analyses, none of our results changed.

A1C and Hemoglobinopathies

A1C depends on the presence of hemoglobin A and, therefore, cannot be measured in the presence of homozygous hemoglobinopathies common in Africa, such as sickle cell anemia, or compound heterozygous hemoglobinopathies such as hemoglobin SC. Because fructosamine and GA are both hemoglobin independent, in theory, they should not be affected by the presence of hemoglobinopathies. In our investigation, no participants had sickle cell disease or hemoglobin SC. Therefore, we cannot assess the diagnostic value of glycated plasma proteins in individuals with homozygous or compound heterozygous hemoglobinopathies. Nonetheless, because the options for diagnosing hyperglycemia in these individuals are limited, generating evidence on whether glycated plasma proteins are effective diagnostic tests in these two groups would be worthwhile.

FPG

We have previously demonstrated that FPG combined with A1C has a significantly greater sensitivity than A1C alone for detecting abnormal glucose tolerance in African immigrants to the U.S. (13). Nonetheless, there are several important reasons why A1C combined with GA is superior to A1C combined with FPG. First, it may not be feasible for a person to get to a medical care site in the morning in the fasted state. Second, the intraindividual variation in FPG concentration is between 5.7 and 8.3% (33); by contrast, the intraindividual variations for fructosamine and GA are 3.4% and 2.1%, respectively. Third, correct handling of a blood sample for glucose is more difficult than for glycated plasma proteins. For glucose, the cells have to be separated from the plasma within 30 min to minimize glycolysis, whereas fructosamine and GA are not affected by glycolysis (33). Fourth, blood glucose values reflect glucose homeostasis at a single point in time, whereas fructosamine and GA are measures of blood glucose concentrations over 14 to 21 days.

Strength and Limitations

The strengths of our study include the absence in our cohort of renal insufficiency, iron deficiency anemia, or hypoalbuminemia. The existence of any one of these conditions might have compromised the interpretation of A1C or GA (34–39). In addition, we were able to obtain data often unavailable in Africa such as VAT.

Furthermore, the age of the African immigrants in the Africans in America cohort (mean 39 ± 10, range 20–64 years) corresponds to the African population at highest risk for prediabetes and diabetes. Globally, most adults with diabetes are between the ages of 40 and 59 years (1). Most people with prediabetes are younger than 50 years of age, and one-third are between the ages of 20 and 39 years (1). Furthermore, 76% of deaths due to diabetes in Africa are in people younger than 60 years (1).

The main limitations of our investigation are the sample size, access to only a single OGTT, and lack of established thresholds for fructosamine and GA. Nonetheless, we are the first to present data on fructosamine and GA as diagnostic tests in Africans. Furthermore, our sample size is comparable to similar analyses of fructosamine and GA performed in other populations (16,28,29,32).

A potential concern is that our study was performed in the U.S. rather than in Africa. Although the prevalence of prediabetes might differ by country of residence, the ability of a test to detect prediabetes should be independent of the continent of residence.

Conclusion

To address the diabetes epidemic in populations of African descent, identifying the people with prediabetes is essential. Accurate assessment will allow for optimal planning and the opportunity to direct interventions to those at highest risk for progression to diabetes. Working with African immigrants living in the U.S., we were able to demonstrate that A1C, fructosamine, or GA identified less than half of the people with prediabetes; however, combining A1C with GA led to the detection of nearly 80% of Africans with prediabetes. By slowing the diabetes epidemic through accurate assessment and early intervention in the prediabetic state, lives could be enhanced, productivity maximized, and health care resources optimized.

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