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# Performance of glycated albumin for type 2 diabetes and prediabetes diagnosis in a South African population

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ABSTRACT

*Objective:* To assess the utility of glycated albumin (GA%) as a diagnostic marker of type 2 diabetes and prediabetes in an African population.
*Methods:* GA% levels were determined in a sample of 1294 mixed ancestry adults (74.2% women) residing in Cape Town using an enzymatic method. The participants' glycemic status was based on oral glucose tolerance test (OGTT).
*Results:* The mean age was 47.8 years with a mean body mass index (BMI) of 28.7 kg/m$^2$. Obesity was more pronounced in the screen-detected diabetes and prediabetes groups with mean BMI's of 32.5 kg/m$^2$ and 31.5 kg/m$^2$ respectively. The optimal thresholds of GA% to diagnose screen-detected diabetes and prediabetes, were 14.90% and 12.75% respectively. For screen-detected diabetes, the C-statistic was higher for HbA1c than GA% ($p$ = .034) with values of 0.899 (95% CI 0.855–0.943) and 0.873 (0.782–0.892) respectively. The agreement between GA% and HbA1c at their optimal thresholds for diagnosing screen-detected diabetes, was *kappa* = 0.33 (95% CI 0.26–0.40) and was higher than the agreement for prediabetes, *kappa* = 0.16 (0.11–0.21). The performance of GA% to identify screen-detected diabetes at the optimal threshold of 14.90%, was 64.8% (95% CI 54.1%–74.6%) for sensitivity and 93.5% (92.0%–94.9%) for specificity. GA% was significantly less sensitive, but more specific than HbA1c (at the optimal threshold of 6.15%) for screen-detected diabetes diagnosis (both $p \leq .002$ from McNemar tests for sensitivity and specificity comparisons).
*Conclusions:* GA% performed less well than HbA1c to identify participants with OGTT-diagnosed type 2 diabetes or prediabetes (HbA1c cut-off of 6.15% and 5.95% respectively) in this population.

## 1. Introduction

Type 2 diabetes is a non-communicable disease (NCD) which is a growing concern worldwide. The worldwide number of people with diabetes is expected to increase by 48% by 2045 from 425 million in 2017 [1]. The highest relative increase is predicted in Sub-Saharan Africa, with an expected 156% increase from 16 million adults in 2017 to 41 million in 2045 [1]. The ADDITION-Europe study stressed the importance of early detection of type 2 diabetes to decrease hyperglycemic and cardiovascular morbidity associated with the condition [2].

The use of glycated proteins for the diagnosis of diabetes and the prediction of diabetes complications has evolved since glycated hemoglobin (HbA1c) was recommended as one of the diagnostic tests for diabetes in 2009 [3]. In diabetes, plasma proteins are exposed to high concentrations of glucose for prolonged periods of time and this leads to protein glycation. Glycation is a non-enzymatic process where the primary and secondary amino acid structure is affected by the addition of

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reducing sugars to their amine groups as opposed to glycosylation which refers to a physiological enzymatic process catalyzed by glycosyltransferases [4,5]. Glycation is a step-wise process and the final products are advanced glycation end-products (AGEs), which play an important role in the pathogenesis of diabetes complications [4,6]. Albumin is the most abundant serum protein and consists of multiple lysine and arginine residues that are involved in glycation [7,8]. Glycated albumin expressed in percentage (GA%) is an intermediate biomarker of glycemic control and has been evaluated for use in patients with haemoglobinopathies, iron deficiency anemia (which are common in Africa) and gestational diabetes where the utility of HbA1c is unreliable [7].

The current study assessed the utility of GA% as a diagnostic tool for type 2 diabetes and prediabetes in a mixed ancestry South African population. We also compared the performance of GA% to that of HbA1c.

## 2. Material and methods

### 2.1. Ethical approval

The original study was approved by the Research Ethics Committees of Cape Peninsula University of Technology (CPUT) and Stellenbosch University (respectively, NHREC: REC - 230,408–014 and N14/01/003). The proposal for the current study was approved by the Ethics Committee of Stellenbosch University (S17/10/259). The study was conducted in accordance with the Declaration of Helsinki. Participation in the study was entirely voluntarily and informed consent was obtained from all participants.

### 2.2. Study population and study design

This was a cross-sectional study involving participants from the ongoing Cape Town Vascular and Metabolic Health (VMH) study. VMH is an extension of the Cape Town Bellville South study, which has been described in detail previously [9,10]. The current study population consisted of 1294 mixed ancestry adults (74.2% women) residing in Bellville-South, Cape Town, South Africa. The baseline examinations for the VMH study were conducted between 2014 and 2016 during a community-based survey. Participants were included if they fasted overnight, had no clinical signs suggestive of recent infection, were not pregnant, and did not use anti-inflammatory drugs within 2 weeks prior to the study. The interviews and data collection were described in detail previously [9]. Blood samples were collected from participants after an overnight fast. Serum was collected in serum separator tubes (Becton Dickinson) and plasma for glucose determination was collected in sodium fluoride tubes (Becton Dickinson). Whole blood for HbA1c determination was collected in potassium-EDTA tubes (Becton Dickinson). The samples were processed within an appropriate time and aliquots were stored at -80 °C. Participants were classified as having either normoglycemia, prediabetes (this included participants with impaired fasting glucose, impaired glucose tolerance or both), known diabetes or screen-detected diabetes based on history, fasting glucose and 2-h glucose post oral glucose tolerance test (OGTT) using the WHO criteria [11]. The current study no sample size estimation was done, instead we included all participants on which the most comprehensive measures of glucose homeostasis were performed and had no known history of diabetes.

### 2.3. Biochemical analysis

GA% was determined with the quantILab® Glycated Albumin assay (Werfen™, Italy, Ref 0018256640) on a Roche® cobas® 6000 analyzer (Roche Diagnostics®, Mannheim, Germany) on serum samples that have been stored at -80 °C. In this assay, the concentration of glycated albumin is determined with an enzymatic method and the concentration of albumin is determined separately with the Bromocresol purple method. GA% is expressed as a percentage and the equation includes an inter-method arithmetic factor for comparability between this method and results obtained by high performance liquid chromatography (HPLC) [12,13]. This method was validated for use on the cobas® 6000 analyzer (Roche Diagnostics®) according to the CLSI EP15-A3 protocol [14]. The within-assay CV was 2.2% and within-laboratory CV was 2.3% for the low concentration control sample (target mean 15.7%) and a within-assay CV of 1.3% and a within-laboratory CV of 1.4% for the high concentration control sample (target mean 37.4%). Bias was evaluated using control samples of known concentrations and was calculated according to the CLSI EP15-A3 guidelines [14]. The bias at a low control concentration was 0.88% and at the high control concentration, 0.36%. The total error observed for high and low concentration control samples were 4.72% and 2.62% respectively. Bias and total error were acceptable according to the desirable analytical goals determined by Montagnana et al. [15].

At the time of screening, an OGTT was performed on all participants and all other biochemical parameters were immediately analyzed at an ISO 15189 accredited Pathology practice (PathCare, Reference Laboratory, Cape Town, South Africa) as previously described [9]. No adverse reaction to OGTT, no serious bleeding following phlebotomy was observed. Blood glucose levels (mmol/L) were determined with an enzymatic hexokinase method (Beckman AU, Beckman Coulter, South Africa) and HbA1c levels were determined with High Performance Liquid Chromatography (HPLC) (BioRad Variant Turbo, BioRad, South Africa). High-density lipoprotein cholesterol (HDL) (mmol/L) was measured by enzymatic immuno-inhibition – End Point (Beckman AU, Beckman Coulter, South Africa), low-density lipoprotein cholesterol (Measured LDL) (mmol/L) by enzymatic selective protection – End Point (Beckman AU, Beckman Coulter, South Africa) and triglycerides (TG) (mmol/L) were estimated by glycerol phosphate oxidase-peroxidase, End Point (Beckman AU, Beckman Coulter, South Africa). Ultrasensitive C-reactive protein (uCRP) was measured by Latex Particle immunoturbidimetry.

### 2.4. Statistical analysis

Data analysis was performed with R statistical software (The R Foundation for Statistical Computing Platform) version 3.4.3 (2017-11-30). Results are reported as count (and percentages), mean (and standard deviation) and median (25th–75th percentiles). The chi square test, analysis of the variance and Kruskal-Wallis test were used to compare baseline characteristics across glucose tolerance subgroups. The covariance estimation of multivariate $t$ distribution was used to calculate the correlation between pairs on continuous measures. This provides some degree of robustness to outliers without giving a high breakdown point. The Williams' test were used to assess the significance of the difference between two dependent correlation coefficients sharing one variable [16]. The association between markers of glucose homeostasis were assessed with segmented regression analysis [17]. This regression technique provides separate regression coefficients for potential piecewise linear relations. Information from the Davies' test for a non-zero difference in slope between variables was used to estimate the breakpoint between two segmented relations [18]. The area under the receiver operating characteristic curve (AUC, C-statistic) was used to assess and compare the ability of GA% and HbA1c to predict the presence of abnormal glucose tolerance [19]. The J-point of Youden was used to derive the optimal cut-off points for the diagnosis of different categories of abnormal glucose tolerance. Kappa statistics were used to assess the agreement between markers at these cut-off points, with the 95% confidence interval (95%CI) computed from 2000 stratified bootstrap replicates, based on the percentiles methods [20]. The performance of GA% and HbA1c at these cut-offs was assessed by computing the following measures of performance (with 95%CI): sensitivity, specificity, Youden's Index, positive predictive value (PPV),

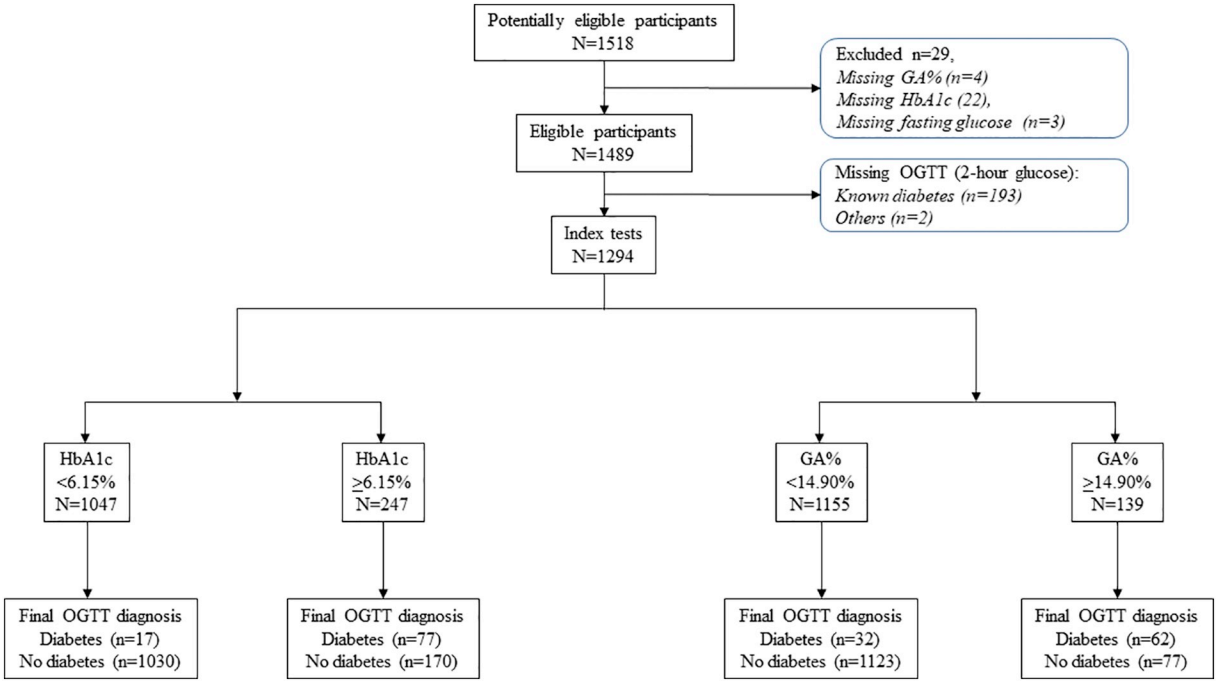


**Fig. 1.** Flow diagram of included participants.

negative predictive value (NPV), accuracy, diagnostic odd ratio (DOR), number needed to diagnose (NND), likelihood ratio of the positive test (LR+) and likelihood ratio of a negative test (LR-). The McNemar test was used to compare the sensitivity and specificity of GA% and HbA1c, which was applied separately to participants with abnormal glucose tolerance (sensitivity comparison) and those without (specificity comparison) based on OGTT [21]. The diagnostic performance of the combination of GA% and HbA1c was also assessed, under the scenario of parallel testing and the assumption of a positive result from any of the tests being equivalent to a positive screening for abnormal glucose tolerance. A two-sided $p$-value < .05 was considered to be statistically significant. The Standards for the Reporting of Diagnostic Accuracy Studies (STARD) was used to report results [22].

## 3. Results

The starting sample included 1518 participants, following which four participants had missing data on GA%. A further 22 participants had missing data on HbA1c, while three had missing data on fasting glucose. Of the remaining 1489 participants, 193 had previously diagnosed diabetes, while two had missing OGTT values. Therefore, the final analytic sample included 1294 participants. Of these participants, 94 (7.3%) had screen-detected diabetes, 223 (17.2%) had prediabetes and 977 (75.5%) were normotolerant (Fig. 1). The characteristics of all the participants according to glycemic status are summarized in Table 1.

Fig. 2 shows the distribution of participants with prediabetes and screen-detected diabetes across increasing fifths of HbA1c and GA% levels for this cohort. The prevalence of screen-detected diabetes demonstrated a significant increase from the lower four fifths to the upper fifth of GA% of between 1.2 and 5.1% to 24.4%. The prevalence of prediabetes did not demonstrate a marked dose-response relationship, with prevalence of between 10.9 and 14.1% in the lower 2 fifths and between 19.1 and 22.1% in the upper 3 fifths. However, for HbA1c there was a marked dose-response response relationship for both screen-detected diabetes and prediabetes. The ability of GA% to classify participants according to glucose tolerance status is summarized in Fig. 3. For screen-detected diabetes, the C-statistic was higher for HbA1c than GA% ($p$ = .034) with values of 0.899 (95% CI 0.855–0.943) and 0.873 (95% CI 0.782–0.892) respectively. For prediabetes HbA1c was also shown to be superior to GA%. HbA1c cut-offs of 6.15% for screen-detected diabetes and 5.95% for prediabetes were identified during receiver operating characteristic (ROC) curve analysis. The optimal thresholds for GA% to diagnose screen-detected diabetes and prediabetes, were 14.90% and 12.75% respectively (Fig. 3). These cut-offs for GA% and HbA1c were used in subsequent analyses. The agreement between GA% and HbA1c at their optimal thresholds for diagnosing screen-detected diabetes, was *kappa* = 0.33 (95%CI 0.26–0.40) and was higher than the agreement for prediabetes, *kappa* = 0.16 (0.11–0.21). Correlation coefficients (95% confidence intervals) of GA% and HbA1c were 0.35 (0.30 to 0.40). GA% had a slightly higher positive predictive value (PPV) of 43.4% (95% CI 34.9–52.1%) versus HbA1c that had a PPV of 30.6% (95% CI 24.8%–36.8%). GA% and HbA1c had similar negative predictive values of 97.2% (95% CI 96.1%–98.1%) and 98.4% (95% CI 97.4%–99.0%) respectively. For prediabetes diagnosis, GA% was more sensitive (67.3% vs. 52.5%), but less specific (51.8% vs. 80.1%) than HbA1c (both $p \leq .0009$), with in general performance measures of the two markers being always lower than those from diabetes prediction (Table 2).

## 4. Discussion

The current study examined the performance of GA% for the diagnosis of diabetes and prediabetes in a high-risk mixed ancestry population. We derived the optimal thresholds of GA% to diagnose screen-detected diabetes and prediabetes and assessed the agreement between GA% and HbA1c in this population. The GA% threshold for screen-detected diabetes was 14.90% and for prediabetes 12.75%. Overall GA% performed less well than HbA1c at diagnosing OGTT-diagnosed diabetes or prediabetes; and was more specific, but less sensitive that HbA1c at the sample-specific optimal thresholds of both markers to detect OGTT-diagnosed dysglycemia in this population. Combining GA% with HbA1c showed no added benefit in this population.

We hypothesized that GA% would be an effective diagnostic test for diabetes and prediabetes in this population, due to the high prevalence

**Table 1**
Characteristics of participants overall and by glucose tolerance status.

| Variables | Overall | Normoglycemia | Prediabetes | Diabetes | p-Value |
|---|---|---|---|---|---|
| N (%) | 1294 (100) | 977 (75.5) | 223 (17.2) | 94 (7.3) | |
| Men, n (%) | 334 (25.8) | 274 (28.0) | 41 (18.4) | 19 (20.2) | 0.005 |
| Age (years) | 47.8 (15.5) | 45.0 (15.3) | 55.1 (13.1) | 59.7 (10.3) | < 0.0001 |
| Fasting plasma glucose (mmol/l) | 5.1 (1.6) | 4.7 (0.5) | 5.4 (0.7) | 8.7 (4.0) | < 0.0001 |
| 2-h glucose (mmol/l) | 6.6 (3.1) | 5.4 (1.3) | 8.7 (1.3) | 14.8 (5.0) | < 0.0001 |
| HbA1c (%) | 5.8 (0.8) | 5.6 (0.5) | 6.0 (0.5) | 7.7 (2.2) | < 0.0001 |
| HbA1c (mmol/mol) | 40 | 38 | 42 | 61 | < 0.0001 |
| Glycated albumin (%) | 13.3 (2.7) | 12.8 (1.3) | 13.2 (1.5) | 18.4 (6.8) | < 0.0001 |
| Albumin (g/l) | 42.4 (2.8) | 42.3 (2.9) | 42.6 (2.6) | 42.3 (2.1) | 0.616 |
| Body mass index (kg/m$^2$) | 28.7 (8.1) | 27.7 (7.8) | 31.5 (8.5) | 32.5 (7.4) | < 0.0001 |
| Waist circumference (cm) | 90 (17) | 88 (16) | 97 (16) | 101 (14) | < 0.0001 |
| Hip circumference (cm) | 103 (16) | 101 (17) | 108 (17) | 109 (14) | < 0.0001 |
| SBP (mmHg) | 127 (25) | 124 (24) | 134 (24) | 137 (25) | < 0.0001 |
| DBP (mmHg) | 81 (14) | 80 (14) | 84 (15) | 85 (15) | < 0.0001 |
| Pulse (bpm) | 70 (12) | 69 (12) | 73 (12) | 75 (14) | < 0.0001 |
| Total cholesterol (mmol/l) | 5.1 (1.2) | 5.0 (1.2) | 5.4 (1.1) | 5.7 (1.2) | < 0.0001 |
| Measured LDL (mmol/l) | 3.2 (1.0) | 3.1 (1.0) | 3.4 (1.0) | 3.7 (0.9) | < 0.0001 |
| HDL (mmol/l) | 1.3 (0.4) | 1.3 (0.4) | 1.3 (0.4) | 1.3 (0.4) | 0.599 |
| Triglycerides (mmol/l) | 1.2 [0.8–1.6] | 1.1 [0.8–1.5] | 1.3 [1.0–1.8] | 1.5 [1.2–2.3] | < 0.0001 |
| uCRP | 3.8 [1.4–8.3] | 3.1 [1.2–7.2] | 5.1 [2.3–10.3] | 6.6 [3.3–15.2] | < 0.0001 |

DBP, diastolic blood pressure; SBP, systolic blood pressure. HDL, high density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; uCRP, ultra-sensitive C reactive protein.

of iron deficiency anemia and the presence of hemoglobinopathies, of which HbS and HbE are the most common [23,24]. Moreover, albumin is a serum protein, the rate at which it is glycated is up to 10 times higher than the rate of hemoglobin glycation and would thus reflect hyperglycemia earlier than HbA1c, allowing for earlier intervention [25]. However, GA% was not more effective than HbA1c to identify OGTT-defined screen-detected diabetes and prediabetes in our population and correlated poorly with HbA1c. These findings are contrast to the much higher correlation coefficients found by other investigators [26–29]. The important differences between our study and others include lack of information with regards to population characteristics, particularly BMI [26,27]. Our study included a high proportion of obese subjects and obesity is a known factor that influences GA% results. Another important factor, is that in our study we used robust approaches that do not make linear assumption, and account for the effect of outliers by down weighting them for instance, leading in general to smaller correlation coefficients than Pearson's correlations. The high mean body mass index (BMI) of 28.7 kg/m$^2$ in the overall sample and over 30 kg/m$^2$ in screen-detected diabetes and prediabetes may be a possible reason for the poor performance of GA% in this population. Previous studies demonstrated an inverse correlation between GA% and BMI [30–32]. A possible theory for this inverse correlation that was suggested by Sumner et al. [30] is that a decrease in total albumin due to obesity-associated inflammation (albumin is a negative acute phase reactant) may be related to a lower GA% [33]. However, in our study there was no significant difference in total albumin concentrations across glucose tolerance statuses. Furthermore, in our study we derived the optimal HbA1c cut-off of 6.15% and used this to assess the performance of HbA1c versus GA%. Juraschek et al. [25] determined HbA1c using a Tina-quant immunoassay method, whereas HbA1c in our study was determined with HPLC (BioRad Variant Turbo).

The optimal GA% threshold for the diagnosis of prediabetes in our population was 12.75%. This cut off is 1% lower than the cut off that was reported by Sumner et al. [30] in an African-American population (≥13.77%). We determined the GA% cut-offs using ROC curves in OGTT-defined participants, whereas the former study determined the GA% cut-off using the recommended HbA1c cut off of 5.7% [30]. We observed that GA% was less sensitive, but more specific than HbA1c in identifying participants with screen-detected diabetes. However, GA% was more sensitive in identifying prediabetes, but less specific than HbA1c. Therefore, GA% may have potential for use in screening programs to detect individuals with prediabetes. Early identification of prediabetes will allow for early lifestyle intervention to prevent progression to diabetes.

The study had several strengths. To our knowledge, this study is the first to assess the performance of GA% in an African population and included a reasonable number of participants. The gold standard for the diagnosis of diabetes and prediabetes was used to classify the participants according to glycemic status. Sample-specific cut-offs for HbA1c and GA% were used for statistical analysis of agreement and performance. The diagnostic performance of GA% was determined using a reliable method, and a wide range of performance measures are

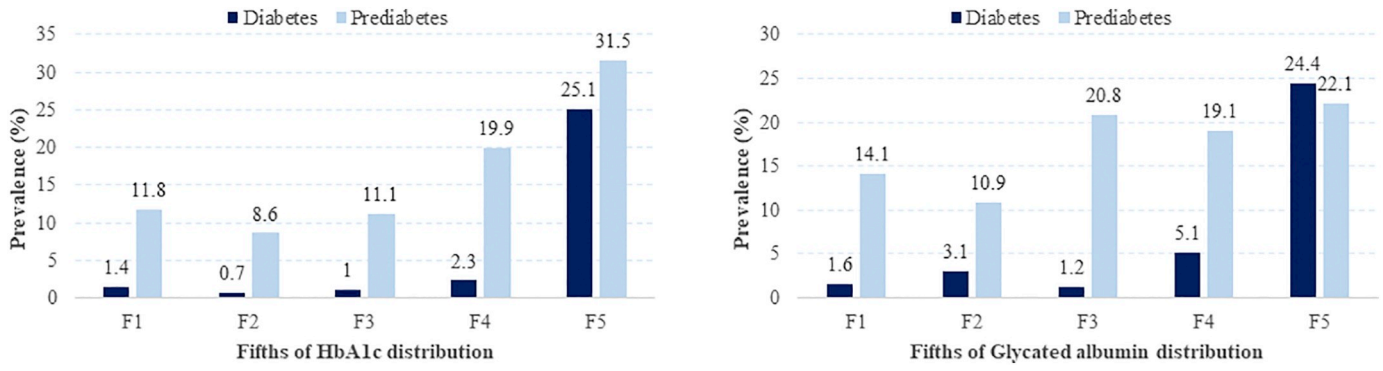


**Fig. 2.** Distribution of diabetes and prediabetes across increasing fifths of the distribution of HbA1c (left) and GA% (right).

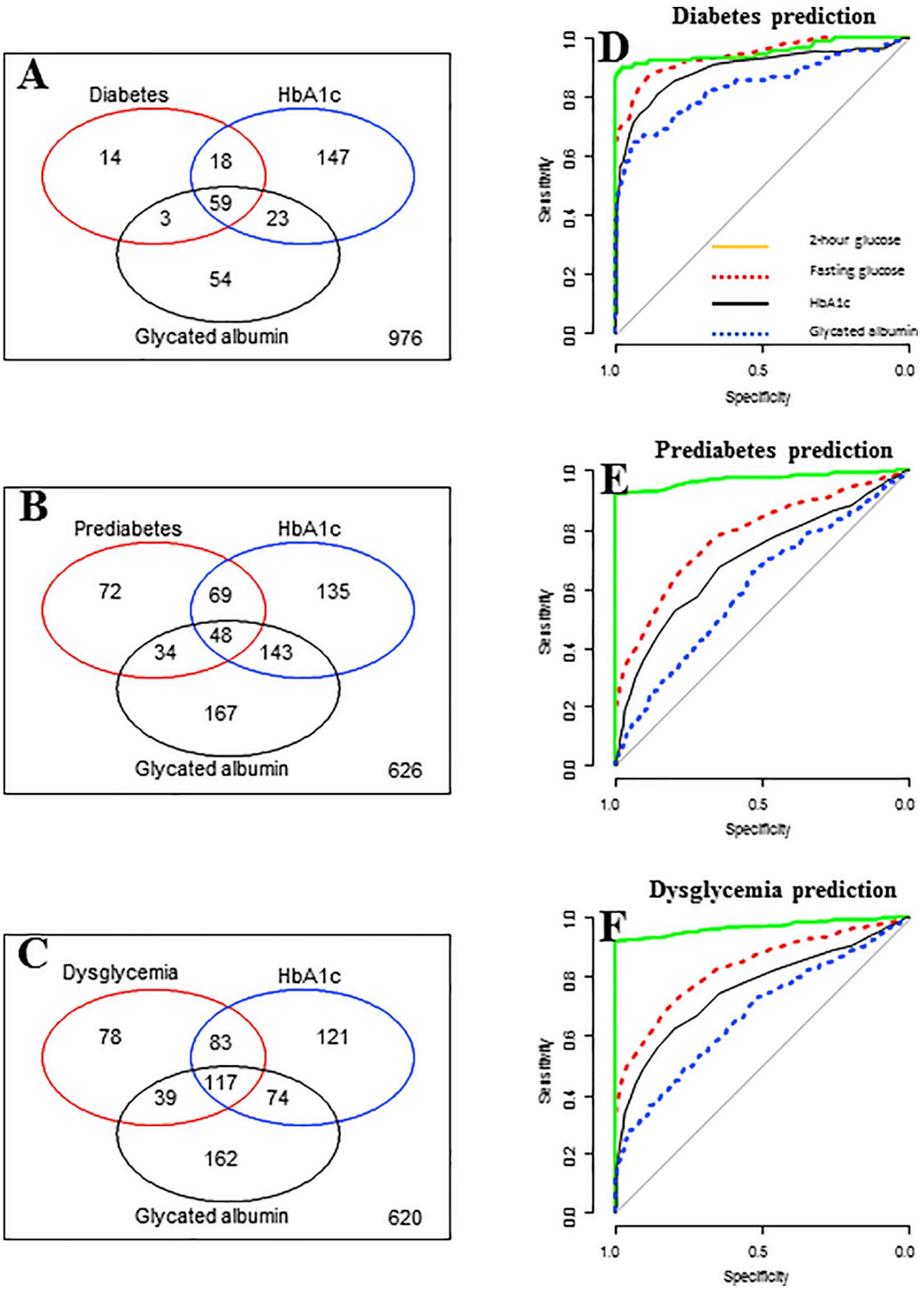


**Fig. 3.** Venn diagrams showing the agreement between HbA1c and GA% at their sample specific threshold to classified various categories of abnormal glucose tolerance as diagnosed by fasting glucose and/or 2-h glucose, and discrimination curves for their prediction by indices of glucose homeostasis.

presented in this paper. The study also had limitations. The current study was limited to an urban mixed ancestry population and may not be representative of other African populations. As we used anonymized data for this study, we were unable to assess the participants' HbA1c reports to determine the presence of hemoglobin variants. The sample consisted of a large proportion of overweight and obese participants with a mean BMI being 28.7 kg/m$^2$. Previous studies demonstrated an inverse correlation between GA% and BMI therefore, the GA% results may have been affected by factors other than glycemic status [30–32]. Due to the cross-sectional nature of this study, we could not investigate the ability of HbA1c and GA% to identify individuals with an increased risk for the development of macro- and microvascular complications. The proportion of males with diabetes did not allow meaningful statistical analysis by sex in this study. GA% was determined on serum samples that were stored at -80 °C, however, it has been demonstrated that GA is stable in stored samples for up to 23 years [34,35].

In conclusion, the performance of HbA1c at a level of 6.15% was superior to GA% in this population. Further investigation is necessary to

**Table 2**
Performance measures of HbA1c and GA% single and in combination at their optimal thresholds.

| Marker/ outcome | Threshold | Apparent prev. | True prev. | Sensitivity | Specificity | Accuracy | DOR | NND | Youden index | PPV | NPV | LR+ | LR- |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Screen-detected diabetes | | | | | | | | | | | | | |
| HbA1c | 6.15 | 18.9 (16.8–21.1) | 7.1 (5.7–8.6) | 81.3 (71.8–88.7) | 85.9 (83.8–87.8) | 85.6 (83.5–87.4) | 26.5 (15.2–46.0) | 1.5 (1.3–1.8) | 67.2 (55.6–76.5) | 30.6 (24.8–36.8) | 98.4 (97.4–99.0) | 5.8 (4.8–6.8) | 0.22 (0.14–0.33) |
| GA% | 14.90 | 10.6 (9.0–12.4) | 7.1 (5.7–8.6) | 64.8 (54.1–74.6) | 93.5 (92.0–94.9) | 91.5 (89.8–93.0) | 26.6 (16.3–43.4) | 1.7 (1.4–2.2) | 58.4 (46.1–69.4) | 43.4 (34.9–52.1) | 97.2 (96.1–98.1) | 10.0 (7.7–13.0) | 0.38 (0.28–0.50) |
| Prediabetes | | | | | | | | | | | | | |
| HbA1c | 5.95 | 26.0 (23.5–28.6) | 18.7 (16.6–21.1) | 52.5 (45.7–59.2) | 80.1 (77.5–82.6) | 75.0 (72.4–77.4) | 4.4 (3.3–6.0) | 3.1 (2.4–4.3) | 32.6 (23.2–41.8) | 37.9 (32.4–43.5) | 88.0 (85.6–90.0) | 2.6 (2.2–3.2) | 0.59 (0.51–0.68) |
| GA% | 12.75 | 51.8 (48.9–54.6) | 18.7 (16.6–21.1) | 67.3 (60.7–73.4) | 51.8 (48.6–55.0) | 54.7 (51.8–57.6) | 2.2 (1.6–3.0) | 5.2 (3.5–10.8) | 19.1 (9.3–28.4) | 24.3 (21.0–27.9) | 87.3 (84.3–89.9) | 1.4 (1.2–1.6) | 0.63 (0.52–0.77) |
| Dysglycemia | | | | | | | | | | | | | |
| HbA1c | 5.95 | 30.4 (27.9–33.0) | 24.5 (22.2–27.0) | 62.7 (57.1–68.1) | 80.1 (77.5–82.6) | 75.9 (73.4–78.2) | 6.8 (5.1–9.0) | 2.3 (2.0–2.9) | 42.9 (34.6–50.7) | 50.6 (45.6–55.7) | 86.9 (84.5–89.0) | 3.2 (2.7–3.7) | 0.46 (0.40–0.54) |
| GA% | 13.64 | 30.0 (27.5–32.6) | 24.5 (22.2–27.0) | 48.7 (43.1–54.4) | 76.1 (73.3–78.8) | 69.4 (66.8–71.9) | 3.0 (2.3–3.9) | 4.0 (3.0–6.1) | 24.8 (16.4–33.2) | 39.8 (34.9–44.9) | 82.0 (79.4–84.5) | 2.0 (1.7–2.4) | 0.67 (0.60–0.75) |

Apparent prev, apparent prevalence; DOR, diagnostic odd ratio; GA%, glycated albumin; LR-, likelihood of a negative test; LR+, likelihood of a positive test; NND, number needed to diagnose; NPV, negative predictive value; PPV, positive predictive value; thresh, threshold; True prev, true prevalence.

assess the utility of GA% in non-obese subjects. The use for GA% should also be evaluated in different clinical scenarios where the use of HbA1c is limited, including patients on dialysis, pregnancy and situations where a rapid change in glucose control is suspected.

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## Author contributions

AEZ: analysis and interpretation of data; co-drafting of the article revising it for important content and final approval of the version to be published. MB: analysis and interpretation of data; co-drafting of the article; final approval of the version to be published APK: analysis and interpretation of data; revising it for important content; final approval of the version to be published. RTE: conception and design of the study revising it for important content; final approval of the version to be published. TEM: conception and design of the study, acquisition of data, revising it for important content; final approval of the version to be published; responsible for ensuring that all authors have agreed 1) to be authors and to be listed in the order specified by the submitting author; 2) to the manuscript's content; and 3) to its submission to the journal.

## Conflict of interest

None declared.

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