Combining HbA1c and glycated albumin improves detection of dysglycaemia in mixed-ancestry South Africans

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Summary

Background Combining HbA1c with glycated albumin (GA) may improve detection of dysglycaemia. As BMI correlates positively with HbA1c and negatively with GA, HbA1c may be more effective in obese and GA in nonobese individuals.

Methods To relate these findings to Africans, we assessed in 1274 South Africans living in Cape Town (male 26%; age 48±16; BMI 28.7 kg/m2 (range 15.6−73.8); obesity 39.9% and no prior diabetes history) the: (1) correlation of BMI with HbA1c and GA, (2) ability of HbA1c and GA separately and jointly, to detect OGTT-diagnosed dysglycaemia (diabetes plus prediabetes). Data collection took place between 2014 and 2016 in the City of Cape Town. Dysglycaemia was diagnosed by glucose criteria for the OGTT. Youden index was used to optimize diagnostic thresholds for HbA1c and GA.

Findings Normal glucose tolerance, prediabetes and diabetes occurred in 76%, 17% and 7%, respectively. BMI positively correlated with HbA1c [r = 0.34 (95%CI: 0.29, 0.39)] and negatively with GA [-0.08 (0.13, 0.03)]. For HbA1c, the optimal threshold by Youden-index for dysglycaemia diagnosis was: 6.0% (95%CI: 5.8, 6.2) and for GA: 13.44% (12.7, 14.71). In the nonobese, obese and total cohort, HbA1c-alone detected: 51% (42, 60), 72% (65, 78), 63% (57, 68), respectively; GA-alone detected 55% (52% (46, 63), 52% (44, 69) and 53% (47, 59), respectively; whereas: HbA1c+GA detected: 69% (60, 76), 82% (75, 87) and 76% (71, 81). Therefore, for the total cohort detection of dysglycaemia HbA1c-alone vs HbA1c+GA detected 63% (57, 68) vs 76% (71, 81).

Interpretation The opposite correlations of HbA1c and GA with BMI have now been demonstrated in an African-based population. Improving detection of dysglycaemia by combining HbA1c and GA has important implications for diabetes risk screening.

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in part the burden of undiagnosed diabetes in Africa.\(^8\) Indeed, the proportion of undiagnosed diabetes is highest in Africa where about 54% of adults living with diabetes are unaware of their condition.\(^7\) Therefore, strategies to contain diabetes in SSA should be twofold and include actions to prevent the development of diabetes in those without the disease, as well as efforts to bring to the medical attention people with diabetes to allow the implementation of interventions to mitigate the risks associated with the condition. For both undertakings, appropriate diabetes risk screening is the reasonable entry point,\(^9\) including in non-obese and young adults who receive little attention in existing screening programs.

The ultimate aim of diabetes risk screening is to uncover both components of dysglycaemia, specifically prediabetes and diabetes.\(^5\) For this purpose, the combination of a fasting glucose and 2 h blood glucose measurements during an oral glucose tolerance test (OGTT) remains the reference standard.\(^9\) Alternative glucose-based tests for dysglycaemia include fasting glucose alone and random blood glucose. The challenges of performing an OGTT in routine settings and issues relating to the preanalytical stability and day-to-day variability of glucose-based tests, have fueled efforts to develop non-glucose-based tests to diagnose dysglycaemia.\(^10,11\) In this regard, glycated haemoglobin (HbA\(_\text{lc}\)) which is the reference standard test to monitor diabetes control, has been promoted in the last decade as diagnostic test for dysglycaemia.\(^12\) However, the relationship of HbA\(_\text{lc}\) with blood glucose is affected by many factors, some of which are race/ethnic or setting specific, resulting in variable performance of HbA\(_\text{lc}\) to diagnose dysglycaemia in diverse populations and settings.\(^13,14\) Furthermore, there is increasing awareness that HbA\(_\text{lc}\) is less effective for screening in non-obese individuals,\(^15,17\) which could make HbA\(_\text{lc}\) a sub-optimal test for dysglycaemia screening in a large proportion of the African population. Glycated albumin (GA) is a ketoamine formed through binding of albumin and glucose by a non-enzymatic glycation reaction. GA reflects short-term average glucose levels (14–21 days) in view of the short half-life of serum albumin, and therefore represents a potential alternative biomarker to monitor glycemic control, particularly in the presence of conditions that make HbA\(_\text{lc}\) measurement unreliable.\(^11,18\) The diagnostic utility of GA for dysglycaemia is also increasingly investigated,\(^19\) with data from Asia suggesting that GA is more effective in non-obese individuals.\(^17,20\) Other suggested diagnostic markers of dysglycaemia include fructosamine.\(^11\)

The few available studies in African populations both within Africa and in the global north have provided mixed results on the performance of HbA\(_\text{lc}\), GA, and fructosamine to diagnose dysglycaemia, with suggestions that none of these tests taken separately matches fasting glucose alone, and that their combination in
parallel does not necessarily enhance their diagnostic performance.\textsuperscript{10,15,21} According to the available evidence, GA is more effective than fructosamine for dysglycemia diagnosis across a broad range of clinical settings,\textsuperscript{2,3} due to a better reproducibility of GA. Emerging data suggest that accounting for the diverging associations of adiposity with HbA\textsubscript{1c} and GA could uncover segments of the populations in which, combining the two biomarkers will enhance diabetes risk screening. This has been demonstrated in African-born Blacks in the US where, adding GA to HbA\textsubscript{1c} resulted in improved detection of dysglycemia in non-obese participants.\textsuperscript{21} However, both the relationship of adiposity with non-glucose-based biomarkers of dysglycemia, and how this relationship affects the diagnostic performance of those biomarkers for dysglycemia, have not been fully investigated in the African setting. Clarifying these issues have relevance, considering the urgent need for tests with optimal diagnostic accuracy for dysglycemia in non-obese Africans.

Therefore, we assessed the correlation of HbA\textsubscript{1c} and GA with BMI and determined the performance of HbA\textsubscript{1c} and GA separately and jointly, to detect OGTT-diagnosed dysglycemia in a large sample of mixed ancestry South Africans in Cape Town.

Methods

Study design, and population

This study uses data from the Cape Town Vascular and Metabolic Health (VMH) cohort, which is an extension of the Cape Town Bellville South study. Both are described in detail elsewhere.\textsuperscript{10,23} The cross-sectional data used were collected between 2014 and 2016, through a population-based survey in the Township of Bellville South in Cape Town. The population is predominantly of mixed-ancestry or coloured (76%) followed by Black Africans (18.5%) and Caucasian and Asians comprising only 1.5% of the total. The study was approved by the Research Ethics Committees of the Cape Peninsula University of Technology (CPUT) and Stellenbosch University (respectively, NHREC: REC - C210 408 – 014 and N14/01/003), and conducted with the code of ethics of the World Medical Association (Declaration of Helsinki). Included participants voluntarily signed a written consent and permission to conduct the study was also obtained from relevant authorities including the city and community authorities.

Interviews and physical examination

Interviews and physical examinations were conducted by trained fieldworkers at a research clinic located within the study suburb. Fieldworkers went door-to-door in the community to distribute fliers to raise awareness of the study and invite potentially eligible participants to take part in the study. Those who volunteered for the study then scheduled for an appointment at our research clinic for further procedures. A day before the scheduled appointment, fieldworkers contacted participants to remind them to fast overnight and confirm the pick-up location. At the clinic, data were collected on demographics, medical histories, ongoing treatments, and habits including smoking using a questionnaire on a password-protected personal digital assistant (PDA). Physical examination involved data collection on blood pressure (BP) using a semi-automatic device (Omron M6 comfort-preformed cuff BP Monitor) and following the World Health Organisation (WHO) guidelines.\textsuperscript{24} BP was measured on the right arm in sitting position and at rest for at least 10 min. The lowest systolic BP (SBP) of three consecutive measures and the corresponding diastolic BP (DBP) were used in all analyses. Body weight (to the nearest 0.1 kg) was measured with the subject in light clothing and without shoes, using an Omron body fat meter HBF-311 digital bathroom scale. Height to the nearest centimeter was measured with a stadiometer, with subjects standing on a flat surface. Body mass index (BMI) was calculated as weight per square meter (kg/m\textsuperscript{2}). Waist circumference was measured with a non-elastic tape at the level of the narrowest part of the torso, as seen from the anterior view. Anthropometric measurements were performed three times and their average used for analysis. Blood samples were collected from all participants after an overnight fast, and two hours after a 75 g OGTT following the WHO recommendations.\textsuperscript{25}

Biochemical analysis

GA was determined with the quantLab\textsuperscript{®} Glycated Albumin assay (Werfen\textsuperscript{TM}, Italy, Ref 0.018,236,640) on a Roche Cobas 6000 analyser (Roche Diagnostics, Mannheim, Germany). In this assay, the concentration of GA 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 of total albumin and the equation includes an inter-method arithmetic factor for comparability between this method and results obtained by high performance liquid chromatography (HPLC).\textsuperscript{26} This method was validated for use on the Cobas\textsuperscript{®} 6000 analyzer (Roche Diagnostics\textsuperscript{®}) according to the CLSI EP15-A3 protocol.\textsuperscript{27} The within-assay CV was 2.2% and within-laboratory CV was 2.3% (bias 0.88%) 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% (bias 0.36%) for the high concentration control sample (target mean 37.4%). The total error observed for high and low concentration control samples were 4.72% and 2.62% respectively.
Articles

Other biochemical parameters were analysed at an ISO 15,189-accredited Pathology practice (PathCare, Reference Laboratory, Cape Town, South Africa). Plasma glucose and HbA1c were measured, respectively, by enzymatic hexokinase method (Beckman AU, Beckman Coulter, South Africa) and NGSP-certified HPLC (Biorad Variant Turbo, BioRad, South Africa). Insulin was determined by a paramagnetic particle chemiluminescence assay (Beckman DXI, Beckman Coulter, South Africa). High-density lipoprotein cholesterol (HDL-C) was by enzymatic immunoinhibition, triglycerides by glycerol phosphate oxidase-peroxidase and low-density lipoprotein cholesterol (LDL-C) by enzymatic selective protection — End Point (Beckman AU, Beckman Coulter, South Africa). Total protein and albumin were determined by immunoturbidimetry on an ABX Pentra 400 (Horiba Medical, USA).

Classification of glucose tolerance status, insulin resistance and adiposity
OGTT glucose values were used as recommended by WHO28 to classify the glucose tolerance status of participants as: 1) normal glucose tolerance (FPG<6.1 mmol/l & 2 h glucose <7.8 mmol/l); 2) prediabetes including impaired fasting glycaemia (IGT, i.e. 6.1≤FPG<7.0 mmol/l), impaired glucose tolerance (IGT, i.e. 7.8<2 h glucose<11.1 mmol/l) and the combination of both; and 3) screen-detected diabetes (FPG≥7.0 mmol/l and/or 2 h glucose≥11.1 mmol/l). Participants were classified according to their BMI as normal weight (BMI <25 kg/m²), overweight (25 kg/m²≤BMI<30 kg/m²) and obese (BMI≥30 kg/m²). Finally, waist circumference (WC) ≥90 cm was used to define abdominal obesity (high WC) in both men and women, in line with previous report from this population.39

The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated according to the formula: HOMA-IR= [fasting insulin concentration (mIU/L) x fasting plasma glucose (mmol/l)]/ 22.5.10

Statistical analysis
The R statistical software (The R Foundation for Statistical Computing Platform) version 4.0.3 (2020–10–10) was used for all data analysis. Results are reported as count (and percentages), mean (and standard deviation) and median (25th–75th percentiles). Baseline characteristics were compared across glucose tolerance subgroups using chi square test, analysis of the variance and Kruskal-Wallis test. 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 significance of the difference between two dependent correlation coefficients sharing one variable was assessed using Williams’ test.37 The ‘robcor’ package was used to assess the effect of controlling for age on partial correlations of BMI with HbA1c and GA.32 The area under the receiver operating characteristic curve (AUC) was used to assess and compare the ability of continuous markers of glucose homeostasis to predict the presence of OGTT-diagnosed abnormal glucose tolerance.33 The AROCsp command of the ‘ROCnReg’ package was used to compute the semi-parametric covariate-adjusted ROC curve.34,35 In order to assess the diagnostic utility of the markers on the same footing, the J-point of Youden was used to derive the optimal cut-off points for the diagnosis of different OGTT-based categories of abnormal glucose tolerance. The performance of markers to diagnosed OGTT-defined abnormal glucose tolerance at these cut-offs was then assessed by computing the following performance measures and accompanying 95%CI: sensitivity, specificity, Youden’s Index, positive predictive value (PPV), 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-). In secondary analyses, we tested the performance of markers at recommended/published thresholds for dysglycaemia which were 5.7% for HbA1c and 14% for GA.15 We also tested the performance of the data-specific 75th percentile (Q3) as diagnostic threshold for HbA1c (6.0%) and GA (13.8%). The diagnostic performance of the combination of markers at their data-specific optimal thresholds (Boolean combinations) 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. The predictive effect of the linear combination of HbA1c and GA was further assessed in logistic regressions, with comparison of three models: covariates only (age, sex and BMI), HbA1c and GA alone, and the combination of HbA1c, GA and covariates. AUC comparison was based on non-parametric methods.31 P-values <0.05 were used to characterise statistically significant results. This study is reported according to the Standards for Reporting of Diagnostic Accuracy Studies (STARD).36

Role of the funding source. The funder had no involvement in the study. APK and TEM had full access to the data and APK took the decision to submit for publication.

Results
General characteristics of the sample
The starting sample included 1518 participants, of which four were removed for missing data on GA. Another 22 participants lack data on HbA1c, whereas three had missing data on fasting glucose. Of the remaining 1490 participants, 193 were previously diagnosed with diabetes, whereas two had missing OGTT values. Therefore, the
The BMI ranged from 15.6 to 73.8 kg/m² (Figure 1, Panels B & C). Controlling for age had no effect on the correlation of BMI with HbA₁c and GA.

Discrimination of dysglycaemia

The C-statistic (95% confidence interval) for the prediction of OGTT-diagnosed diabetes by markers of glucose homeostasis in the overall sample was: fasting glucose 0.940 (0.910–0.967), 2 h glucose 0.960 (0.929–0.990), HbA₁c 0.899 (0.855–0.944) and GA 0.842 (0.787–0.896); with non-significant difference between fasting and 2 h glucose (p = 0.381), fasting glucose and HbA₁c (p = 0.081), and HbA₁c and GA (p = 0.050). Withing BMI categories, GA performed less well than HbA₁c in normal weight and overweight participants (both p<0.033) whereas both markers had similar performance among obese participants (p = 0.402).

For the prediction of dysglycaemia (the combination of diabetes and prediabetes), 2 h glucose always outperformed all other markers as expected, whereas fasting glucose performed equally with HbA₁c and GA in overweight, but outperformed them in normal-weight and obese; and HbA₁c did better than GA only in the overall sample and among obese participants (Table 2). The continuous predictive ability of HbA₁c and GA for dysglycaemia is shown in Figure 2. There was no indication of perfect diagnostic cut-off.

The prediction of diabetes and dysglycaemia within WC categories is also summarized in Table 2, with again estimates of c-statistics and patterns of differences across markers in participants with abdominal obesity and those without, mirroring respectively those observed in participants with general obesity, while effect sizes and patterns in participants without abdominal obesity (WC<90 cm) were in line with those seen in the normal weight group or in the combined normal weight and overweight group. Due to these consistent similarities, no further analyses by WC categories were conducted.
Figure 1. Histogram and superimposed normal curve for the distribution of body mass index (BMI) in the overall sample (Panel A), and Correlation of BMI with HbA1c (Panel B) and glycated albumin (Panel C) in the overall sample and by diabetes status.

For the correlation plots (B and C), the correlation coefficients and accompanying 95% confidence intervals (95%CI) are shown overall and separately for participants with diabetes and those without. All correlations are statistically significant except for BMI vs. glycated albumin in people with diabetes, where the 95%CI include the absolute zero.
Estimates of the discrimination after adjustment for covariates are shown in Supplemental Table 2. Adjustment for BMI enhanced the discrimination power of GA for dysglycaemia, but attenuated the discriminatory ability of other markers; while adjustment for age and sex, with and without BMI systematically attenuated the discriminatory power of all biomarkers. The effect of covariates on the discrimination was less important for 2 h glucose than the other three biomarkers.

Performance of GA and HbA₁c at their optimal threshold, and in linear combinations

By the Youden’s index the optimal threshold for dysglycaemia diagnosis by HbA₁c was 5.95% (5.75 to 6.15) and for GA was 13.44% (12.72 to 14.71). Optimal thresholds for other outcomes coding are shown in Supplemental Table 3. The sensitivity at optimal threshold to diagnose dysglycaemia in the overall sample was 63.0 (57.4–68.4) for HbA₁c-alone, 53.0 (47.3–58.7) for GA-alone and 76.2 (71.1–80.8) for the combination of HbA₁c and GA, Figure 3. Equivalent figures were: non-obese 50.8 (41.0–59.6), 54.6 (45.6–63.4) and 68.5 (59.7–76.3); and obese 71.8 (64.7–78.2), 51.9 (44.4–59.4) and 81.8 (75.4–87.1); Figure 3, Supplemental Table 3 and Supplemental Figure 2. The characteristics of participants with dysglycaemia and those without across different combinations of HbA₁c and GA ate their optimal thresholds, are shown in Supplemental Table 4, with suggestions of differential distribution of age and blood pressure levels.

The performance of HbA₁c and GA at recommended/published threshold as well as while using the 75th percentile of their distribution as threshold to diagnose dysglycaemia is described in Supplemental Table 3. Patterns of performance measures were broadly similar those observed at the optimal thresholds.

Discussion

Analyses in this large sample of mixed-ancestry South Africans confirmed the positive correlation of BMI and HbA₁c and the negative correlation of BMI and GA.

Table 1: General characteristics of the sample by body mass index (BMI) status.

| Variable                          | Overall | Normal weight | Overweight | Obese | p-value² |
|-----------------------------------|---------|---------------|------------|-------|----------|
| N (%)                             | 1274 (100) | 492 (38.6)    | 273 (21.4) | 509 (39.9) | 0.001    |
| Female, n (%)                     | 946 (74.2) | 281 (57.1)    | 203 (74.4) | 462 (90.8) | <0.001   |
| Age, years                        | 47.8 (15.7) | 44.1 (16.1)   | 48.0 (15.1) | 51.3 (14.3) | <0.001   |
| BMI, kg/m²                        | 28.7 (8.0) | 21.1 (2.3)    | 27.4 (1.5) | 36.7 (5.9) | <0.001   |
| Waist circumference, cm           | 90 (17) | 75 (9)        | 89 (8)     | 105 (12) | <0.001   |
| Hip circumference, cm             | 103 (16) | 89 (9)        | 101 (7)    | 117 (13) | <0.001   |
| SBP, mmHg                         | 127 (24) | 123 (26)      | 127 (23)   | 131 (23) | <0.001   |
| DBP, mmHg                         | 81 (14) | 78 (16)       | 80 (13)    | 84 (13) | <0.001   |
| Total cholesterol, mmol/L         | 5.1 (1.2) | 4.8 (1.1)     | 5.4 (1.2)  | 5.3 (1.1) | <0.001   |
| Measured LDL, mmol/L              | 3.2 (1.0) | 2.8 (0.9)     | 3.4 (1.1)  | 3.4 (1.0) | <0.001   |
| HDL Cholesterol, mmol/L           | 1.34 (0.38) | 1.45 (0.45)   | 1.31 (0.32) | 1.25 (0.30) | <0.001   |
| Median Triglycerides, mmol/L (Q1-Q3)| 1.16 (0.84–1.65) | 0.94 (0.71–1.33) | 1.24 (0.91–1.80) | 1.35 (1.01–1.88) | <0.001 |
| HbA₁c, % (SD)                     | 5.8 (0.8) | 5.6 (0.6)     | 5.8 (0.7)  | 6.0 (1.0) | <0.001   |
| Fasting glucose, mmol/L (SD)      | 5.1 (1.4) | 4.7 (0.9)     | 5.1 (1.1)  | 5.5 (1.8) | <0.001   |
| 2 h glucose                       | 6.7 (3.2) | 5.7 (2.6)     | 6.6 (2.8)  | 7.6 (3.5) | <0.001   |
| Glucose tolerance status          | <0.001   |               |            |        |          |
| Normal                            | 963 (75.6) | 422 (85.8)    | 213 (78.0) | 328 (64.4) | 0.001    |
| Prediabetes                       | 221 (17.3) | 53 (10.8)     | 43 (15.7)  | 125 (24.6) | 0.001    |
| Diabetes                          | 90 (7.1) | 17 (3.4)      | 17 (6.2)   | 56 (11.0) | 0.001    |
| Glycated albumin, % (SD)          | 13.2 (2.4) | 13.1 (1.8)    | 13.2 (2.2) | 13.3 (3.0) | 0.351    |
| Albumin, g/L (SD)                 | 42.4 (2.8) | 42.4 (3.2)    | 42.9 (2.8) | 42.1 (2.4) | 0.030    |
| HOMA-IR                           | 1.4 (0.8–2.3) | 0.8 (0.5–1.3) | 1.4 (1.0–2.0) | 2.2 (1.4–3.5) | <0.001 |
| Variables/outcomes | C-statistic (95% CI) | C-statistics comparison (p-values) | Optimal threshold |
|-------------------|----------------------|----------------------------------|-------------------|
|                   | Vs. 2-h              | Vs. HbA1c                        | Vs. GA            |
| Screen-detected diabetes (N = 1274) |                       |                                  |                  |
| Overall sample (n = 1274) |                       |                                  |                  |
| FBG (mmol/l)      | 0.940 (0.910–0.967)  | 0.381                            | 0.0013            | 5.65 (5.45–5.85) |
| 2-h glucose (mmol/l) | 0.960 (0.929–0.990)  | 0.018                            | <0.0001           | 10.55 (10.25–11.10) |
| HbA1c (%)         | 0.899 (0.855–0.944)  | 0.050                            |                  | 6.15 (6.05–6.45) |
| Glycated albumin (%) | 0.842 (0.787–0.896) |                                  |                  | 14.90 (13.68–15.28) |
| Normal weight (n = 492) |                       |                                  |                  |
| FBG (mmol/l)      | 0.884 (0.804–0.964)  | 0.093                            | 0.607             | 5.45 (4.65–5.85) |
| 2-h glucose (mmol/l) | 0.971 (0.922–1.000)  | 0.020                            | 0.074             | 11.25 (8.25–11.55) |
| HbA1c (%)         | 0.763 (0.598–0.929)  | 0.188                            |                  | 5.85 (5.75–6.55) |
| Glycated albumin (%) | 0.852 (0.734–0.969)|                                  |                  | 14.58 (13.10–15.24) |
| Overall sample (n = 1274) |                       |                                  |                  |
| Normal + Overweight (n = 765) |                       |                                  |                  |
| FBG (mmol/l)      | 0.910 (0.823–1.000)  | 0.071                            | 0.893             | 5.85 (5.85–6.50) |
| 2-h glucose (mmol/l) | 1.000                | 0.033                            | 0.093             | 11.35 (11.10–11.95) |
| HbA1c (%)         | 0.907 (0.946–0.998)  | 0.218                            |                  | 6.35 (5.95–6.55) |
| Glycated albumin (%) | 0.906 (0.796–1.000) |                                  |                  | 13.94 (13.88–16.34) |
| Obese (n = 509)   |                       |                                  |                  |
| FBG (mmol/l)      | 0.973 (0.894–0.987)  | 0.273                            | 0.016             | 5.75 (5.55–6.80) |
| 2-h glucose (mmol/l) | 0.933 (0.877–0.989)  | 0.402                            | 0.001             | 10.55 (10.02–11.11) |
| HbA1c (%)         | 0.990 (0.859–0.956)  | 0.024                            |                  | 6.45 (6.05–6.65) |
| Glycated albumin (%) | 0.828 (0.758–0.897) |                                  |                  | 14.90 (13.30–15.62) |
| Normal waist (n = 658) |                       |                                  |                  |
| FBG (mmol/l)      | 0.972 (0.788–0.957)  | 0.099                            | 0.323             | 5.25 (4.95–5.65) |
| 2-h glucose (mmol/l) | 0.973 (0.925–1.000)  | 0.023                            | 0.033             | 11.35 (8.25–11.65) |
| HbA1c (%)         | 0.792 (0.646–0.939)  | 0.679                            |                  | 6.15 (5.75–6.35) |
| Glycated albumin (%) | 0.824 (0.700–0.948) |                                  |                  | 13.81 (13.67–15.24) |
| High waist (n = 616) |                       |                                  |                  |
| FBG (mmol/l)      | 0.958 (0.932–0.984)  | 0.733                            | 0.0008            | 5.85 (5.75–6.25) |
| 2-h glucose (mmol/l) | 0.948 (0.905–0.992)  | 0.234                            | 0.0003            | 10.55 (10.25–11.10) |
| HbA1c (%)         | 0.919 (0.879–0.960)  | 0.023                            |                  | 6.35 (6.15–6.45) |
| Glycated albumin (%) | 0.853 (0.794–0.912) |                                  |                  | 14.12 (13.38–15.16) |
| Dysglycemia (n = 1274) |                       |                                  |                  |
| Overall (n = 1274) |                       |                                  |                  |
| FBG (mmol/l)      | 0.830 (0.801–0.859)  | <0.0001                          | 0.0006            | 5.15 (5.05–5.35) |
| 2-h glucose (mmol/l) | 0.968 (0.953–0.983)  | <0.0001                          | 0.0001            | 7.75 (7.75–7.75) |
| HbA1c (%)         | 0.765 (0.731–0.799)  | <0.0001                          |                  | 5.95 (5.75–6.15) |
| Glycated albumin (%) | 0.673 (0.637–0.710) |                                  |                  | 13.44 (12.72–14.71) |
| Normal weight (n = 492) |                       |                                  |                  |
| FBG (mmol/l)      | 0.826 (0.768–0.884)  | 0.0004                           | 0.0004            | 4.95 (4.75–5.15) |
| 2-h glucose (mmol/l) | 0.961 (0.923–0.998)  | <0.0001                          | 0.0001            | 7.75 (7.75–7.75) |
| HbA1c (%)         | 0.663 (0.584–0.742)  | 0.879                            |                  | 5.85 (5.65–6.05) |
| Glycated albumin (%) | 0.657 (0.580–0.734) |                                  |                  | 13.67 (12.84–14.74) |
| Overweight (n = 273) |                       |                                  |                  |
| FBG (mmol/l)      | 0.742 (0.659–0.825)  | <0.0001                          | 0.975             | 5.15 (5.05–3.45)* |
| 2-h glucose (mmol/l) | 0.994 (0.986–1.000)  | <0.0001                          | 0.0001            | 7.45 (7.15–7.75)* |
| HbA1c (%)         | 0.744 (0.664–0.823)  | 0.393                            |                  | 5.95 (5.75–5.95)* |
| Glycated albumin (%) | 0.704 (0.628–0.780) |                                  |                  | 13.06 (12.72–13.68)* |

Table 2 (Continued)
Furthermore, the correlation of both markers with fasting and 2-h glucose was dependent on adiposity with point estimates consistently increasing across increasing BMI categories. The discriminatory ability of the two markers for prevalent dysglycaemia was better in obese than in non-obese participants. At their respective data-specific optimal threshold for dysglycaemia diagnosis, performance measures were mostly better for HbA1c than GA, whereas combining the two markers improved sensitivity, particularly in non-obese participants. Nonetheless, we continue to recommend the simultaneous measurement of HbA1c and GA independent of BMI because in any given clinical setting BMI may not have been properly calculated or a factor which compromises HbA1c interpretation such as anemia may be present and undiagnosed. Similarly, hypoalbuminemia is not routinely assessed and may be present compromising GA interpretation.

The correlations of HbA1c and GA with fasting and 2-h glucose have been previously investigated including in African populations.15-30 In the latter however, the effects of adiposity on the correlations have been seldom investigated.30 The correlation of HbA1c and GA with each other and with glucose-based markers in our sample was low-to-modest, with estimates being better for HbA1c than GA against glucose-based tests. In analyses stratified by BMI status estimates significantly improved in obese participants, with substantial attenuation of the HbA1c vs. GA differences. This confirms recent findings in Black South Africans and supports the suggestion that these biomarkers could become more relevant for glucose tolerance status assessment with the increasing obesity in Africa.40 However, the rather modest correlation of the two biomarkers argues against their interchangeability for this purpose.

The diverging association of HbA1c and GA with BMI, which was apparent in our population, has been described in previous studies,15,20,41-45 with the negative association of GA with BMI attributed to increased albumin catabolism from obesity-related chronic inflammation,41 and defective insulin secretion and subsequent post-prandial hyperglycemia.44,45 In short, if obesity-induced inflammation affects GA levels for reasons other than degree of glycemia, GA cannot be used to assess glycemia in the obese.

Our cohort was characterized by the availability of the full range of the BMI distribution from 15 to 74 kg/m² (Figure 1, Panel A), allowing a comprehensive assessment of the relationships of BMI with HbA1c and GA. Variable strengths of those relationships have been reported in existing studies. One such study has for instance reported a one kg/m² higher BMI to be associated with a 0.13% decrease in GA,20 which is compatible with the significant positive correlation found in our sample.

HbA1c has been promoted as biomarkers for glucose tolerance status classification for over a decade.9,11,12 However, studies on the performance of HbA1c in

### Table 2: Discrimination of indices of glucose homeostasis for dysglycaemia diagnosis.

| Variables/outcomes | C-statistic (95% CI) | C-statistics comparison (p-values) | Optimal threshold |
|--------------------|----------------------|-----------------------------------|-------------------|
|                    |                      | Vs. 2-h                           | Vs. HbA1c          | Vs. GA.            |
| Normal + overweight (n = 765) |                      |                                    |                   |
| FBG (mmol/l)       | 0.795 (0.747–0.842)  | <0.0001                           | 0.006             | 0.0004            | 5.05 (4.95–5.15)* |
| 2-h glucose (mmol/l)| 0.975 (0.953–0.996)  | <0.0001                           | <0.0001           | 0.775             | 7.75 (7.15–7.75)* |
| HbA1c (%)          | 0.705 (0.649–0.761)  |                                    | 0.359             | 5.75 (5.65–5.95)* |
| Glycated albumin   | 0.677 (0.622–0.731)  |                                    |                   |                   | 13.17 (12.82–13.68)* |
| Obese (n = 509)    |                      |                                    |                   |
| FBG (mmol/l)       | 0.840 (0.801–0.878)  | <0.0001                           | 0.027             | <0.0001           | 5.25 (5.15–5.35)* |
| 2-h glucose (mmol/l)| 0.954 (0.930–0.979)  | <0.0001                           | <0.0001           | 7.65 (7.65–7.75)* |
| HbA1c (%)          | 0.787 (0.743–0.830)  |                                    | 0.0009            | 5.95 (5.95–6.05)* |
| Glycated albumin   | 0.692 (0.643–0.741)  |                                    |                   |                   | 13.02 (12.72–13.3)* |
| Normal waist (n = 658) |                      |                                    |                   |
| FBG (mmol/l)       | 0.804 (0.751–0.857)  | <0.0001                           | 0.0007            | 0.0006            | 4.95 (4.85–5.15)  |
| 2-h glucose (mmol/l)| 0.969 (0.938–0.999)  | <0.0001                           | <0.0001           | 7.75 (7.75–7.75)  |
| HbA1c (%)          | 0.671 (0.603–0.738)  |                                    | 0.820             | 5.95 (5.65–6.15)  |
| Glycated albumin   | 0.663 (0.598–0.727)  |                                    |                   |                   | 13.52 (12.74–14.78) |
| High WC (n = 616)  |                      |                                    |                   |
| FBG (mmol/l)       | 0.821 (0.783–0.858)  | <0.0001                           | 0.064             | <0.0001           | 5.35 (5.25–5.75)  |
| 2-h glucose (mmol/l)| 0.961 (0.942–0.981)  | <0.0001                           | <0.0001           | 7.75 (7.75–7.75)  |
| HbA1c (%)          | 0.779 (0.738–0.819)  |                                    | 0.001             | 6.05 (5.95–6.35)  |
| Glycated albumin   | 0.697 (0.652–0.741)  |                                    |                   |                   | 12.94 (12.72–14.23) |

95% CI, 95% confidence intervals; FBG, fasting blood glucose; GA, glycated albumin; 2-h, 2 h glucose; WC, waist circumference.
African populations have been inconsistent. This has been ascribed at least in part to the high prevalence in the African setting of interfering factors/conditions that can affect the diagnostic utility of HbA1c. These factors include among others ethnic differences in HbA1c levels, the high burden of infectious diseases such as HIV and tuberculosis, anemia of various etiologies, and hemoglobin variants. One recent systematic review has concluded that the commonly advocated threshold for diabetes of \( >6.5\% \), HbA1c will substantially misclassified the status of many African people for dysglycaemia, while HbA1c>6.0% was associated with the highest sensitivity for OGTT-diagnosed diabetes mellitus.

GA responds faster than HbA1c to increases in glucose levels, and therefore could be a potentially sensitive biomarker of early stages dysglycaemia. Few studies on the performance of GA to diagnose dysglycaemia in African populations have been consistent in showing a modest performance of GA, with comparative studies suggesting that GA is less sensitive but more specific than HbA1c. Beside adiposity, one study has suggested age, gender and ethnicity to be potential determinants of GA levels in African populations. But the potential impact of these factors on the performance of GA to diagnose dysglycaemia in African populations has yet to be explored. A systematic review and meta-analysis of worldwide studies on the diagnostic performance of GA concluded based on 16 eligible studies that the optimal threshold was 14.0%. This threshold was associated with a sensitivity of 76.6% and a specificity of 68.7%. There was however substantial heterogeneity across included studies, reflecting the diversity of the populations across studies, but also the spectrum of

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assays used to measure GA across studies. Indeed, unlike HbA1c, there are currently no international standards for GA measurement.

Our teams have in two previous studies in African-born Blacks living in America, shown that combining HbA1c and GA resulted in improved sensitivity to diagnose dysglycaemia than using HbA1c alone. In one of the studies, we have further demonstrated that this increase in sensitivity was primarily driven by improved performance in nonobese participants. While this pattern was also apparent in the current study, due to the largely overweight and obese profile of our sample (mean BMI 28.7 kg/m²), the advantage of combining HbA1c and GA to diagnose dysglycaemia would apply across the entire population. Internationally, attention has focused primarily on the combination of HbA1c with fasting glucose for abnormal glucose tolerance diagnosis. Accordingly, data is currently lacking on the combined performance of HbA1c and GA in diverse settings.

Our study has major strengths. It is the first detailed study on the effect of adiposity on the performance of HbA1c and GA in Africa, and it is the largest study to investigate those issues in any populations of African descent. Some limitations should also be accounted for while interpreting the findings from our study. The sample was restricted to mixed-ancestry adults residing in an urban environment, which may therefore not be representative of the diverse African population. We lacked data on the presence of haemoglobin variants and other factors than can interfere with HbA1c and/or GA measurement, and were therefore unable to account for their possible effects on the observed findings. However, haemoglobinopathies are much less common in southern African countries than West, Central and East Africa. The low representation of men in our sample precluded sex-specific analyse and therefore, our findings are largely driven by the performance of the HbA1c and GA in women.

In conclusion, the population of people with diabetes and other forms of dysglycaemia is rapidly increasing in Africa, against a background of very low detection rates, inviting more effort into the development for better screening tests for diabetes in these populations. The many challenges associated with implementing OGTT preclude its widespread application. Our study supports previous suggestions that whereas HbA1c and GA are not optimal for dysglycaemia screening when only one is used, combining these two markers could become increasing important for dysglycaemia screening in African populations. Both HbA1c and GA are non-fasting biomarkers and this enhances their ease of administration. Population-based screening for common chronic infectious disease in Africa such as HIV is already taking place across many settings on the continent using minimally invasive blood sample collection. Adding HbA1c and GA provides an opportunity to co-screen people for dysglycaemia.

**Contributors**

Funding acquisition (APK, TEM, RTE), Study conception (APK, TEM, RTE, AES), operationalization and supervision of data collection (TEM), data analysis and

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**Figure 3.** Sensitivities of HbA1c and glycated albumin (GA) singly and in combination for the diagnosis of dysglycaemia in the overall sample (panel A), and separately in non-obese (panel B) and obese participants (panel C).

The black boxes are for the effect estimates (sensitivity), with the absolute value displayed next to each box. The vertical bars about the black boxes are for the 95% confidence intervals.
interpretation and drafting of the manuscript (APK, AES), critical revision of manuscript (TEM, RTE, DBS, AEZ), approval of the final version (all co-authors).

APK and TEM had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis; both are guarantors.

Data sharing statement
The data can be accessed from the corresponding author upon a reasonable request, and subject to approval by the Ethics Communities. The original approval for this data collection did not make provision for data sharing.

Declaration of interests
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Supplementary materials
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