Lack of association of glycated haemoglobin with blood pressure and subclinical atherosclerosis in black South Africans: a five-year prospective study

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Abstract

Objectives: Hypertension and diabetes are common in rapidly urbanising sub-Saharan African communities. However, lack of longitudinal data in these regions prevents adequate analysis of the link between measures of glycaemia and cardiovascular disease. Therefore, we examined the relationships of fasting glucose and glycated haemoglobin (HbA_{1c}) with brachial and central blood pressure (BP), and measures of vascular structure and function after five years in black South Africans.

Setting and subjects: Nine hundred and twenty-eight participants were included as part of the Prospective Urban Rural Epidemiological (PURE) study in the North West Province.

Outcome measures: Fasting glucose, HbA_{1c} and brachial BP at two time points were determined. Central BP, augmentation index (AI) and carotid intima-media thickness (CIMT) were taken at follow-up.

Results: Fasting glucose [4.78 (3.50, 6.30) vs. 5 mmol/l (3.96, 6.42)]; HbA_{1c} [5.6 (4.9, 6.3) vs. 5.9% (5.2, 6.9) and (37 vs. 41 mmol/mol)]; and BP (134/88.1 vs. 138/89.5 mmHg) increased significantly over five years (p-value < 0.05). However, an association was absent between BP, AI or CIMT and either baseline or the five-year change in glucose or HbA_{1c}. Multivariate analyses confirmed that neither glucose or HbA_{1c} predicted changes in BP, CIMT or AI, but factors that did associate significantly were age, male gender, rural location, abdominal obesity, alcohol intake, total cholesterol to high-density lipoprotein ratio, C-reactive protein and antihypertensive medication (R^2, ranging from 0.24-0.36).

Conclusion: Although both BP and measures of glycaemia increased significantly over five years in black South Africans, glucose was not independently associated with BP or measures of large artery structure or function. We suggest that fasting glucose and HbA_{1c} below the threshold of diagnosing diabetes should not be used in isolation to predict cardiovascular risk in African individuals.

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Introduction

Cardiovascular disease is a major cause of death in sub-Saharan Africa. Hypertension and diabetes mellitus are the leading culprits.[1] Hypertension is twice as common in patients with type 2 diabetes than it is in patients without it,[2] which indicates a strong link between hypertension and chronically elevated glucose. Maruthur et al reported that black African American participants were more likely to have higher chronic glucose levels, as measured by glycated haemoglobin (HbA_{1c}), than white participants.[3] This may indicate an elevated risk of cardiovascular disease.

Previously, the prevalence of type 2 diabetes in Africa was rare. The famous Dr Cook said: "Diabetes is very uncommon, but very fatal" in his notes on disease in Africa.[4] However, recent evidence indicates an increasing incidence and prevalence of type 2 diabetes mellitus throughout Africa, which has accompanied rapid urbanisation.[5-7] This implies severe consequences with regard to cardiovascular morbidity and mortality.

Although basic research has implicated an association between cardiovascular function and glucose, limited information is available on this association in longitudinal epidemiological studies on black South Africans. In an

attempt to address these issues, we aimed to confirm whether or not measures of glycaemia and blood pressure (BP) increased significantly over a five-year period in black South Africans. Secondly, we assessed whether or not baseline and the five-year change in glycaemic status (as measured by fasting glucose and HbA_{1c}), were associated with BP, subclinical atherosclerosis and cardiovascular function.

Method

Study design

The Prospective Urban Rural Epidemiological (PURE) study is a multinational, longitudinal study, particularly pertaining to low- and middle-income countries, including South Africa.[8,9] The data used in this study form part of the baseline data collected in the South African leg of the PURE study that was performed in North West province in which 1 004 rural, and 1 024 urban participants, took part. Follow-up data collection took place in 2010, in which 1 279 subjects participated. Our specific substudy was embedded within the South African PURE study, and included 928 volunteers with baseline and follow-up data, who were older than 32 years of age, from urban (Ikageng; Potchefstroom) and rural (Ganyesa, Moswana and Tlakgameng; Vryburg) environments, with no plans of moving in the future, and who were not pregnant or lactating. Subjects infected with the human immunodeficiency virus (HIV) (n = 212), and making use of diabetes medication (self-reported) (n = 66) were excluded from this study. There was a good gender and locality distribution in the final group. Sixty-three per cent were women and 58% lived in rural, rather than urban settlements.

During recruitment, the protocol was explained in the subjects' home language, and each participant was given an opportunity to ask questions. Afterwards, if an individual wanted to participate, written informed consent forms were obtained. Ethical approval for the study was obtained from the Ethics Committee of North-West University, which adheres to the principles of the 2008 Declaration of Helsinki. Subjects received pre- and post-counselling with regard to HIV testing. Data were treated confidentially, and laboratory and data analyses performed using anonymous numbers.

Organisational procedures

Participants were collected from their communities by the research team, and after a 10- to 15-minute drive, arrived at the research facility at approximately 07h30. An introduction to the set-up, an explanation of the procedures and counselling on HIV were given, and the informed consent forms signed. Lifestyle and demographic data were obtained by trained fieldworkers using a standardised questionnaire in the participants' language. Lifestyle data included tobacco use, alcohol intake, health history and medication use.

Anthropometric measurements

Anthropometric measurements were obtained using the guidelines adopted from the National Institutes of Health-sponsored 1988 Arlie Conference. The subjects wore minimal or no clothing during the evaluation. Weight was measured to the nearest 0.1 kg. Weight was determined when the subjects were barefoot, using a portable digital Precision Health Scale® (A & D Company, Tokyo, Japan). Height was measured to the nearest millimetre in the upright standing position using an IP 1465® stadiometer (Invicta, London, UK). Waist circumference (WC) was measured over the abdomen between the costal margin and the iliac crest. Measurements were taken to the nearest millimetre, using a nonstretchable standard Holtain® tape (Apex Tool Group, Apex, USA).

Cardiovascular measurements

Brachial BP was recorded using the validated Omron® HEM-757 (Omron Healthcare, Tokyo, Japan) automatic digital BP monitor on the right arm, after the subject had been in the sitting position for at least 10 minutes, at baseline and during follow-up data collection. Two measurements were taken with the right arm elevated to heart level, at five-minute intervals. Obtained cardiovascular variables included systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) and heart rate. Some cardiovascular measurements were only determined at follow-up, including central SBP and augmentation index (AI), which were measured using the Omron® HEM-9000AI (Omron Healthcare, Tokyo, Japan). Carotid intima-media thickness (CIMT) was obtained using a SonoSite® Micromaxx (SonoSite Inc, Washington, USA) and a 6- to 13-MHz linear array transducer. Images from at least two optimal angles of the left and right common carotid artery were obtained. Following previous prescribed protocols,[10] these segments were imaged and measured. A single reader conducted measurements using a semi-automated programme, namely the Artery Measurement Systems® II v1.139 (Chalmers University of Technology, Gothenburg, Sweden).

Blood sampling and biochemical analyses

A registered nurse collected blood from the brachial vein branches, using a sterile, winged infusion set and syringes, with minimal stasis before 12h00 to minimise the effects of diurnal variation. The subjects were asked to fast overnight (8-10 hours with no food or beverages,

excluding water). The blood was centrifuged for 15 minutes (2 000 g at 4°C). Aliquots of plasma were frozen on dry ice, and stored in the field at -18°C for 2-4 days, after which the samples were transported to a storage facility where they were kept at -82°C until analysis. Glycated HbA_{1c} measurements were determined on-site on ethylenediaminetetraacetic acid (EDTA)-treated whole blood using the D-10 Hemoglobin Testing System® (#220-0101) from Bio-Rad Laboratories, Hercules, USA. This system is based on the use of ion-exchange, high-performance liquid chromatography to separate the different types of haemoglobin which are measured as they pass through a filtre photometer at 415 nm. The system was calibrated once a week using the D-10™ HbA_{1c} Calibrator/Diluent set (#220-0118), (Bio-Rad Laboratories) while Lypochek® Diabetes (# 740) control samples (Bio-Rad Laboratories) were run once a day. High-sensitivity C-reactive protein (CRP) was measured using a Synchron® LX System (Beckman Coulter Inc, Fullerton, USA) and the Cobas® Integra 400 Plus System (Roche, Indianapolis, USA). Plasma glucose, gamma glutamyl transferase (GGT) and the lipid profile [total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol] were measured using the Konelab® 20i (Thermo Scientific, Vantaa, Finland) and the Cobas Integra 400 Plus System instruments. HIV status was determined on the day of the data collection by a First Response Rapid HIV® card test (PMC Medical, Daman, India). In the event of a positive outcome, the result was confirmed with the Pareeshak® card test (BHAT, Bio-tech, India) at baseline, and with the Sensa® HIV 1/2 Test (Seyama Solutions, Johannesburg, South Africa) at year five.

Statistical analyses

Data were statistically analysed by means of Statistica® version 10 (Statsoft Inc, Tulsa, USA). Variables that were not normally distributed were logarithmically transformed (fasting glucose, HbA_{1c}, GGT and CRP). The five-year changes in continuous variables were determined using dependent t-tests. The McNemar test was employed for categorical variables. Multivariate forward stepwise regression analyses were used to assess the association between the different cardiovascular variables as dependant variables (either the five-year percentage change in SBP, DBP, and PP; or CIMT, central SBP and AI, which were only taken at follow-up). Independent variables included age, gender, rural or urban location, tobacco and antihypertensive medication use at baseline, baseline BP (either systolic, diastolic or PP as appropriate), baseline, and the percentage change in HbA_{1c}, WC, TC to HDL ratio, GGT and CRP. Similar models were performed where baseline and the percentage change in HbA_{1c} were replaced with baseline and the percentage change in fasting glucose levels as main independent variables.

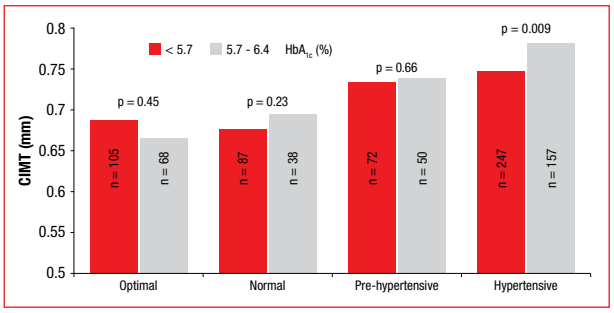
Results

To address our first aim, we outlined the anthropometric, cardiovascular and biochemical characteristics of the study participants (n = 928) over the five-year follow-up (Table I). As expected, brachial BP increased significantly, by approximately 4 mmHg for SBP, over five years. In addition, a significantly greater number of subjects were receiving antihypertensive therapy at the five-year follow-up. Fasting glucose also increased by an approximate 0.22 mmol/l, supporting an increase of 0.38% in HbA_{1c} (p-value < 0.001). This significant

Table I: Anthropometric, cardiovascular and biochemical characteristics of study participants over a five-year period (n = 928)

Characteristics	2005	2010	p-value
Age (years)	50.8 ± 9.88	55.4 ± 9.91	< 0.001
Anthropometric measurements			
Weight (kg)	63.9 ± 17.3	65.4 ± 18.2	< 0.001
Body mass index (kg/m^2)	25 ± 7.18	25.7 ± 7.53	< 0.001
Waist circumference (cm)	80 ± 12.8	81.9 ± 13.2	< 0.001
Cardiovascular measurements			
Systolic blood pressure (mmHg)	134 ± 24.3	138 ± 24.1	< 0.001
Diastolic blood pressure (mmHg)	88.1 ± 14.5	89.5 ± 13.7	0.004
Pulse pressure (mmHg)	46.2 ± 15.1	48 ± 16.2	0.001
Central systolic blood pressure (mmHg)	-	149 ± 24.5	
Augmentation index (%)*	-	92.7 ± 11.8	
Carotid intima-media thickness (mm)		0.73 ± 0.15	
Anti-hypertensive medication (%)	9.59	35.3	< 0.001
Smoking (%)	54.4	57.7	< 0.001
Biochemical measures			
Fasting glucose (mmol/l)	4.78 (3.50-6.30)	5 (3.96-6.42)	< 0.001
Glycated haemoglobin A_{1c} (%)	5.6 (4.9-6.3)	5.9 (5.2-6.9)	< 0.001
Glycated haemoglobin A_{1c} (mmol/mol)	37 (30-45)	41 (33-52)	< 0.001
Total cholesterol to high-density lipoprotein ratio	1.04 ± 1.23	1.16 ± 2.36	0.16
Gamma glutamyl transferase (U/l)	55.5 (19.4-366)	45.1 (12.3-315)	< 0.001
C-reactive protein (mg/l)	3.09 (0.25-39.8)	3.42 (0.29-31.9)	0.0062

Data are arithmetic mean ± standard deviation and geometric mean (95th percentile intervals) for logarithmically transformed variables.
* Adjusted for heart rate



CIMT: carotid intima-media thickness, HbA_{1c}: haemoglobin A_{1c}
p-values refer to differences between carotid intima-media thickness categories of individuals with haemoglobin A_{1c} ranging between 5.7% and 6.4% and individuals with lower haemoglobin A_{1c} values within each blood pressure category
(Participants with haemoglobin A_{1c} > 6.5% or 48 mmol/mol were excluded owing to the small sample size)

Figure 1: Carotid intima-media thickness according to baseline blood pressure and haemoglobin A_{1c} categories

increase in HbA_{1c} was found, irrespective of gender and urban versus rural location (not shown).

We performed single linear regression analyses between cardiovascular measurements (ΔSBP, ΔDBP, ΔPP, central SBP, CIMT and AI) and baseline HbA_{1c}, as well as the percentage change in HbA_{1c}. Baseline HbA_{1c} correlated significantly (r = 0.15, p-value < 0.001) with CIMT at follow-up, but we found no other significant correlation between any cardiovascular measurement and either baseline or the percentage change in HbA_{1c}. We explored the association between HbA_{1c} and CIMT further by dividing participants according to BP and HbA_{1c} categories (< 5.7% and 5.7-6.4%) (Figure 1). There were no significant differences in CIMT between both HbA_{1c} groups within optimal to prehypertensive BP categories (p-value > 0.23). Hypertensive individuals with HbA_{1c} values ranging between 5.7% and 6.4% had significantly higher CIMT than participants with lower HbA_{1c} levels (p-value 0.009).

In multivariate stepwise regression analyses (Tables II and III), with changes in brachial BP or follow-up central SBP, CIMT or AI as dependent variables, the main independent variable, HbA_{1c}, was not significantly associated with the dependent variables. Overall, age, gender, WC, the percentage change in WC and rural versus urban location were the most significant predictors of the various cardiovascular measurements (as dependant variables). We also repeated all six models in Tables II and III, and replaced HbA_{1c} (baseline and percentage change) with fasting glucose (baseline and percentage change). All of the results were identical (not shown) as for HbA_{1c}, i.e. without inclusion of glucose in the final models. The only exception was for the model with percentage PP as a dependent variable. In this model (R^2 = 0.24), the percentage change in fasting glucose (β = -0.06, p-value 0.22) contributed to a variance in percentage change in PP.

Sensitivity analyses

We also made use of additional regression models to confirm the absence of an association between cardiovascular measures and HbA_{1c}. Forward stepwise regression was carried out to assess the association between baseline HbA_{1c} and baseline SBP, DBP and PP. We also performed forward stepwise regression analyses with similar models to those in Tables II and III, except these was performed separately in groups, namely urban, rural, men or women. HbA_{1c} did not enter the model in any of these.

Discussion

Unsurprisingly, our study demonstrated significant increases in fasting glucose and HbA_{1c} levels in black

Table II: Forward stepwise regression analyses with five-year percentage change in systolic blood pressure, diastolic blood pressure or pulse pressure as dependant variables (n = 928)

Characteristics	ΔSystolic blood pressure (%)		ΔDiastolic blood pressure (%)		ΔPulse pressure (%)	
	R^2 = 0.26		R^2 = 0.36		R^2 = 0.24	
Age (years)	β 0.09	p-value 0.005	β -0.05	p-value 0.07	β 0.18	p-value 0.001
Gender (M, W)	β -0.08	p-value 0.009			β -0.10	p-value 0.002
Rural, urban	β -0.09	p-value 0.003	β -0.06	p-value 0.02	β -0.07	p-value 0.023
WC (cm)	β 0.06	p-value 0.05	β 0.14	p-value < 0.001		
ΔWC (%)	β 0.07	p-value 0.02	β 0.09	p-value 0.001		
SBP (mmHg)	β -0.53	p-value < 0.001	-		-	
DBP (mmHg)	-		β -0.57	p-value < 0.001	-	
PP (mmHg)	-		-		β -0.51	p-value < 0.001
A-HP meds (no or yes)	β 0.04	p-value 0.16				
TC: HDL ratio					β 0.05	p-value 0.071
ΔGGT (%)			β 0.13	p-value < 0.001	β -0.06	p-value 0.041

A-HP meds: anti-hypertensive medication, β: beta, DPB: diastolic blood pressure, GGT: gamma glutamyl transferase, HDL: high-density lipoprotein, M: men, PP: pulse pressure, SBP: systolic blood pressure, TC: total cholesterol, W: women, WC: waist circumference

Table III: Forward stepwise regression analyses with central systolic blood pressure, carotid intima-media thickness, or augmentation index as dependent variables (n = 928)

Characteristics	Central SBP		CIMT (mm)		Augmentation index (%)	
	$R^2 = 0.31$		$R^2 = 0.31$		$R^2 = 0.16$	
Age (years)	β 0.12	p-value < 0.001	β 0.43	p-value < 0.001	β 0.06	p-value 0.053
Gender (M, W)			β -0.17	p-value < 0.001	β 0.32	p-value < 0.001
Rural, urban	β -0.13	p-value < 0.001				
WC (cm)			β 0.12	p-value < 0.001	β -0.28	p-value < 0.001
ΔWC (%)	β 0.05	p-value 0.122	β 0.05	p-value 0.087	β -0.05	p-value 0.114
SBP (mmHg)	β 0.51	p-value < 0.001	β 0.14	p-value < 0.001		
A-HP meds (no or yes)					β 0.09	p-value 0.010
Smoke (no or yes)					β 0.11	p-value 0.001
TC: HDL ratio					β 0.07	p-value 0.028
ΔTC: HDL ratio	β -0.04	p-value 0.160				
GGT (log U/l)			β -0.06	p-value 0.040	β 0.10	p-value 0.005
ΔGGT (%)					β 0.05	p-value 0.118
CRP (log mg/l)			β 0.07	p-value 0.032		
ΔCRP (%)	β -0.04	p-value 0.162				

A-HP meds: anti-hypertensive medication, β: beta, CIMT: carotid intima-media thickness, CRP: C-reactive protein, GGT: gamma glutamyl transferase, HDL: high-density lipoprotein, M: men, SBP: systolic blood pressure, TC: total cholesterol, W: women, WC: waist circumference

South Africans over a five-year period, independent of gender and rural or urban location. This increase was accompanied by significant increases in BP, thereby confirming previous observations.[11,12]

Our most prominent finding was that despite the parallel elevations in both HbA_{1c} and BP over five years, neither the baseline nor the five-year change in HbA_{1c} was associated with an elevation in BP or PP. In addition, HbA_{1c} was also not linked to measures of vascular structure and function (CIMT and AI) and central SBP that were taken at follow-up. In support of the findings on HbA_{1c}, fasting glucose levels were also not linked to a change in BP or vascular structure and function.

These weak results are unexpected when viewed in the light of previous findings. More than a decade ago, Coutinho et al showed that there was a progressive relationship between glucose levels and cardiovascular risk below the threshold for diabetes in a meta-regression analysis of 95 783 men without diabetes.[13] However, another carefully designed study by Temelkova-Kurktschiev et al suggested that a weak association existed between fasting plasma glucose and CIMT in individuals without diabetes.[14] The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study group included 22 cohorts in Europe, and concluded that the relationship between mortality and glucose was a J-shaped curve, rather than one that showed a threshold effect at high glucose levels. However, the relation between cardiovascular disease mortality and two-hour plasma glucose was graded and kept on increasing.[15]

With much less evidence available for HbA_{1c} as a measure of glycaemic status, it is assumed that the progressive relationship and J-shaped curve that were found between plasma glucose and cardiovascular disease risk and mortality[13,15] is also applicable to HbA_{1c} and cardiovascular disease risk. However, in a large prospective study, Pradhan et al found that although HbA_{1c} predicted diabetes in normoglycaemic women, its association with incident cardiovascular events was low, and was largely attributable to coexistent risk factors.[16] Our multiple regression results seem to support their findings, where other risk factors, such as age, male gender, rural location, abdominal obesity, excessive alcohol use, dyslipidaemia and inflammation all contributed significantly to the five-year change in BP, as well as CIMT and AI. However, when we explored CIMT according to BP and HbA_{1c} categories in Africans without diabetes, the synergistic effects of hypertension and HbA_{1c} contributed to a significant elevation in CIMT (Figure 1), which was not seen in prehypertensives, or those with lower BP or HbA_{1c}. This supports recent findings by Paynter et al that cardiovascular risk prediction in patients with diabetes was improved by incorporating HbA_{1c} in prediction models.[17]

The addition of a measure of glucose to improve prediction models is expected because of the well-known effects of glucose on a mechanistic level. Hyperglycaemia inhibits major antioxidant systems (the interacting glutathione and thioredoxin system),[18] that leads to an increased production of free radicals,[19,20] and also results in impaired endothelium-dependent

vasodilation of the micro- and macrocirculation through inhibition of endothelial nitric oxide synthase activity.[21-24] Therefore, glucose may causally relate to vascular dysfunction and atherosclerosis through various mechanisms that are evident in the literature.

Nevertheless, in our study, we did not find an independent relationship between HbA_{1c} and BP or CIMT over five years. The reason for this absent link is unclear, but we expect that chronic hyperglycaemia exerts certain effects on the vasculature that may only be observed over a longer follow-up period.

Our results suggest that the effects of hyperglycaemia on vascular deterioration take longer in Africans, but this needs to be confirmed in future studies. This result is especially surprising because of the known link between hyperinsulinaemia and salt sensitivity which has been demonstrated in black populations.[25,26] In our study, we did not measure salt sensitivity or insulin levels. Therefore, future studies should include these measures to identify the causal pathways that underlie the development of both diabetes and cardiovascular disease in black South Africans.

This study should be viewed within the context of its strengths and limitations. The strengths include the longitudinal study design which included HbA_{1c} and advanced cardiovascular measures in a large sample of 928 African individuals. Weaknesses are that several measurements (central SBP, CIMT and AI) were not taken at baseline, and that a longer follow-up period may have been required. Glycaemia was not assessed with an oral glucose tolerance test which might have assisted in better understanding the level of glycaemia in our population. Our sample was also selected from specific areas where unemployment is common. The applicability of our results to groups with a higher socio-economic class should be confirmed.

Conclusion

Despite parallel elevations of fasting glucose, HbA_{1c} and BP over five years in a sample of 928 Africans, no independent association between either baseline or the five-year change in glycaemic status and BP and CIMT were found. Our results suggest that fasting glucose and HbA_{1c} below the threshold for diagnosing diabetes should not be used in isolation to predict cardiovascular risk in African individuals.

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