

Carotid intima-media thickness and its associations with type 2 diabetes mellitus in South Africans

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Abstract

Objectives: Carotid intima-media thickness (CIMT) is a surrogate marker of subclinical atherosclerosis and a predictor of cardiovascular events. Few studies in Africa have evaluated CIMT and its associations in people with type 2 diabetes mellitus. This study measured CIMT in a sample of mainly black South African patients with type 2 diabetes mellitus, and evaluated the association of demographic and clinical risk factors with CIMT.

Design: Cross-sectional study.

Setting: Kafalong Hospital, a large community hospital in Pretoria that mainly serves an urban black community.

Subjects: Patients with type 2 diabetes mellitus.

Outcome measures: We evaluated clinical, biochemical and CIMT ultrasound measurements in a standardised fashion.

Results: In 185 patients, the univariate significant predictors of mean far-wall CIMT were age [beta 0.007 (standard error 0.001)], systolic blood pressure [beta 0.001 (standard error 0.000)] and inverse serum creatinine [beta -8.15 (standard error 3.23)]. Low-density lipoprotein cholesterol, apolipoprotein A-1, apolipoprotein B:A-1 ratio and apolipoprotein B:A-1 ratio > 1.2 all had p-values below 0.1, but above 0.05. Age had the largest R-squared (20%). The multivariate models did not explain more of the variation in CIMT than did age alone.

Conclusion: Lipid parameters were related to CIMT in our study population. However, this did not reach statistical significance in this relatively small sample, and lipids added very little to the variability of CIMT compared with age alone.

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Introduction

In South Africa, no long-term prospective outcome studies have evaluated cardiovascular outcomes in patients with diabetes mellitus. Whether or not imaging of subclinical atherosclerosis results in better cardiovascular risk prediction is debatable, but a recent systematic review found that measurements such as carotid intima-media thickness (CIMT) may add predictive value in asymptomatic individuals at intermediate cardiovascular risk.¹

CIMT measurements have been linked to both prevalent and incident coronary artery disease or events, as well as white matter lesions, strokes and all-cause mortality.²⁻¹¹ Age- and sex-adjusted risk of incident stroke or myocardial infarction increased more than twofold in cardiovascular health study

participants whose mean maximal common CIMT measurements were greater than 1.18 mm (based on one longitudinal image on B-mode ultrasound on the left and right side).¹² Recently, the maximum internal and mean common CIMT both predicted cardiovascular outcomes in the Framingham Offspring Study cohort.¹³

In a systematic review, Brohall et al found CIMT to be 0.13 mm thicker in patients with type 2 diabetes mellitus compared to that in subjects without diabetes.¹⁴ Lee et al¹⁵ and Haffner¹⁶ established that this increase was higher in subjects with overt macroangiopathic complications.

Risk factors that have been associated with CIMT are age, smoking, hypertension and diabetes.¹⁷ Studies have shown associations between low-density lipo-

protein (LDL) cholesterol, as well as high-density lipoprotein (HDL) cholesterol and CIMT. It seems that the particle size of the LDL is a better predictor of CIMT than LDL alone.¹⁸⁻²⁰ In 1999, the Atherosclerosis Risk in Communities Study (ARIC) study found that the association between CIMT and LDL, HDL and other lipid measurements was significantly weaker in African-American, compared to white subjects.²¹

More recently, the interest shifted to the apolipoprotein B (ApoB) to apolipoprotein A-1 (ApoA-1) ratio as a predictor of cardiovascular risk. In a cohort study with follow-up as long as 8.9 years, multivariate analyses revealed that only the ApoB:ApoA-1 ratio and serum insulin were significantly related to CIMT progression rate. (HDL and the non-HDL:HDL ratio were also in the final multivariate model, but were no longer statistically significant.)²² Associations that have been found between kidney function and CIMT have varied. Some studies²³⁻²⁵ found a link between albuminuria and CIMT, whereas others found one with estimated glomerular filtration rate (eGFR), but not with albumin excretion rates.²⁶ Cystatin C was demonstrated to be associated with cardiovascular events in a community-based Chinese population,²⁷ and in patients with type 1 diabetes mellitus it was connected with coronary artery disease progression.²⁸ In middle-aged adults, cystatin C was found not to be linked to CIMT.^{29,30}

We could only find one study that evaluated CIMT in South African black patients, in which Holland et al assessed CIMT in black patients with suspected coronary artery disease. There was a significant positive linear trend between CIMT and the number of affected coronary vessels (p -value < 0.0001, $r = 0.44$).³¹ The aim of our study was to determine CIMT and its associations with demographic and clinical variables in a group of South African patients with type 2 diabetes mellitus.

Method

Ethics committee approval and funding

The protocol (104/2005) was approved by the University of Pretoria Ethics Committee. All participants gave their written consent. The study was funded by the University of Pretoria.

Setting and patient selection

A convenience sample of 185 patients with type 2 diabetes mellitus was recruited from the Kalafong Hospital Diabetes Clinic, which mainly serves the black urban population of Atteridgeville and Saulsville, in the Tshwane metropole.

Measurements

Patient demographics and disease history were obtained using a standardised questionnaire. Blood

pressure was measured after at least five minutes of sitting with an appropriate cuff size using a Baumanometer mercury sphygmomanometer. Weight was determined using a balance scale (Detecto Scales, USA) and waist circumference (site of minimal circumference on anterior-posterior diameter) was measured using a flexible tape measure. CIMT was determined using a standardised protocol. Two ultrasonographers were trained and certified as CIMT sonographers by the Julius Centre, Utrecht University, the Netherlands.

The CIMT measurements (Sonosite 180) using a linear 10-5 MHz transducer included bilaterally common carotid scans at four standardised 30-degree incremental angles using the Meijer Carotid ARC,³² as well as an assessment of the carotid bulb and internal carotid for the presence and severity of plaque. The CIMT was defined as the distance between the leading edges of the lumen interface and the media-adventitia interface at the far wall. The CIMT was expressed as the mean value of the measurements at a predefined location in the distal common carotid, just before the widening of the bifurcation (10 mm proximal to the tip of the flow divider). The average of the mean far-wall CIMT for all angles on both sides was then calculated. Plaque presence was assessed as plaque being present in the common carotid, the bifurcation and the internal carotid if visualised by the ultrasonographers and confirmed when the offline CIMT was determined. The formal Mannheim criteria³³ for plaque were not used. (Formal analysis of plaque and its associations will be carried out at a later stage.)

A sample of 20 patients was evaluated by both ultrasonographers. The coefficient of variation within subjects was 2.5% for the far-wall measurements. The CIMT scans were measured offline using the Artery Measurement System (Image & Data Analysis Company, Sweden) software.³⁴ The mean of all the far-wall CIMT measurements was used for analyses.³⁵

Non-fasting blood samples for lipids (Friedenwald equation used), ApoA-1 and ApoB, cystatin C, haemoglobin A_{1c} (HbA_{1c}) and serum creatinine were collected, together with urine for the albumin:creatinine ratios. Blood and urine chemistry was measured at the hospital laboratory using the Dimension RXL analyser (Siemens). eGFR was calculated using a formula that had been validated on black South Africans as $175 \times (\text{serum creatinine} \times 0.0113)^{-1.154} \times (\text{age})^{-0.203} \times (1 \text{ if male and } 0.724 \text{ if female})$.³⁶ Knowing that our LDL measurements would not be valid in non-fasting samples, we also measured apolipoproteins that did not require fasting samples. The apolipoproteins were measured after specimens had been frozen at -70°C and analysed with the IMMAGE immunochemistry

system using the apolipoprotein calibrator at a central National Health Services laboratory. Likewise, cystatin C (also on specimens that had been frozen at -70°C) was measured nephelometrically on the same system using the DAKO reagent.

Descriptive statistics were used to describe the sample. Linear regression was used to determine significant associations with CIMT. Regression analysis was performed to assess independent associations with CIMT (explanatory model). Associations with CIMT that had a p -value < 0.25 were included in multivariable linear regression analyses. A p -value < 0.05 was regarded as statistically significant.

Variables were transformed if transformation generated residuals with a normal distribution. Variables that could not be normalised were categorised. The model was reduced in a stepwise backward fashion, deleting the variable with the highest p -value, while observing the change in R-squared. Following the multivariable regression analyses, regression diagnostics were performed to evaluate the assumptions for linear regression and to detect outliers.

Results

The evaluated patients (Table I) were mostly women (71%), with hypertension (87%). Only a few patients smoked (8%) or had existing cardiovascular disease (17%). Fifty-two per cent of the patients were on insulin and 24% were on a statin at the time of evaluation.

Univariate associations with far-wall carotid intima-media thickness where p -value < 0.25 , are shown in Table II.

The mean near- and far-wall CIMT were 0.84 mm (0.17) and 0.82 mm (0.17) respectively. Thirty-six per cent of patients had plaque at any site, left or right. The CIMT between those with a history of cardiovascular disease (angina, myocardial infarction, angiogram, amputation and stroke) and those without was not significantly different [mean difference 0.067 standard error (0.035), p -value = 0.054].

Univariate linear regression analyses revealed that age, systolic blood pressure, a family history of diabetes, a family history of hypertension and inverse serum creatinine levels were statistically significantly associated with far-wall CIMT. Age had the strongest relationship with CIMT (20% of the variation observed in CIMT could be explained by age). However, additional variables (all with p -value < 0.25) were evaluated in the multivariable model. Patients with plaque, as could be expected, had thicker CIMT, but plaque was not used in the multivariable model.

The final multivariable models are shown in Table III. We did not use the lipid parameters together in one

Table I: Description of the study sample (n = 185)

Variable	n (%)	Mean (SD)	Median (IQR)
Gender			
Male	54 (29.19)		
Female	131 (70.81)		
Race			
Asian	18 (9.73)		
Black	161 (87.03)		
Coloured	3 (1.62)		
White	3 (1.62)		
Other			
Age (years)		60.65 (11.25)	
Diabetes duration (years)			10 (5-15)
Hypertension	161 (87.03)		
Hypertension duration (years)			8 (2-15)
Systolic blood pressure (mmHg)		141.90 (24.38)	
Diastolic blood pressure (mmHg)		86.82 (14.36)	
Waist circumference		101.94 (11.88)	
Body mass index		31.74 (6.76)	
Current smoker	15 (8.11)		
Cardiovascular disease positive	26 (141.00)		
Laser therapy history positive	20 (10.81)		
Monofilament sensation impairment	47 (25.41)		
On insulin	97 (52.43)		
On statin	44 (23.91)		
Mean near-wall CIMT (mm)		0.84 (0.17)	
Mean far-wall CIMT (mm)		0.82 (0.17)	
Plaque anywhere (CCA, BIF, ICA)	67 (36.20)		
Serum creatinine ($\mu\text{mol/l}$)	184		74 (64.89-90)
eGFR ($\text{ml/minute}/1.73 \text{ m}^2$)	184	74.71 (23.34)	
Urine microalbumin: creatinine ratio	164		2.10 (0.80-7.50)
Cystatin C (mg/l)	173	1.14 (0.40)	
Apolipoprotein A-1 (g/l)	173	1.30 (0.33)	
Apolipoprotein B (g/l)	173	1.03 (0.32)	
Serum triglycerides (mmol/l)	184		1.30 (0.90-1.90)
Serum LDL (mmol/l)	178	3.01 (0.96)	
Serum HDL (mmol/l)	184	1.13 (0.37)	
% HbA _{1c}	184	8.59 (2.42)	
Serum cholesterol (mmol/l)		4.85 (1.15)	

BIF: bifurcation, CIMT: carotid intima-media thickness, CCA: common carotid artery, eGFR: estimated glomerular filtration rate, HbA_{1c}: haemoglobin A_{1c}, HDL: high-density lipoprotein, ICA: internal carotid artery, IQR: interquartile range, LDL: low-density lipoprotein, SD: standard deviation

Table II: Univariate associations with far-wall carotid intima-media thickness where p-value < 0.25

Variable	Beta (change in CIMT in mm)	SE	p-value	95% CI	R ² (% change in CIMT explained)
Age (years)	0.007	0.001	0.000	0.005 to 0.009	0.200
Diabetes duration > 10 years (median) (vs. ≤ 10 years)	0.037	0.024	0.126	-0.011 to 0.085	0.013
Hypertension duration > 8 years (median) (vs. ≤ 8 years)	0.046	0.024	0.058	-0.002 to 0.094	0.020
Systolic blood pressure (mmHg)	0.001	0.000	0.040	0 to 0.002	0.023
On aspirin therapy	0.031	0.024	0.208	-0.017 to 0.079	0.009
Cardiovascular event history ("No" omitted)	0.040	0.032	0.217	-0.024 to 0.103	0.008
Body mass index	-0.003	0.002	0.060	-0.007 to 0.0001	0.020
Cystatin C (mg/l)	0.043	0.032	0.176	-0.020 to 0.107	0.010
Serum creatinine (inverse)	-8.149	3.232	0.013	-14.525 to -1.772	0.034
eGFR (ml/minute/1.73m ²)	-0.002	0.0005	0.001	-0.003 to -0.001	0.056
ApoA-1 (g/l)	-0.066	0.040	0.098	-0.143 to 0.012	0.020
ApoB:ApoA-1 ratio	0.081	0.044	0.068	-0.006 to 0.169	0.019
ApoB/ApoA-1 > 1.2	0.052	0.029	0.079	-0.006 to 0.109	0.020
Serum LDL (mmol/l)	0.023	0.013	0.085	-0.003 to 0.048	0.017
Plaque present	0.120	0.024	0.000	0.073 to 0.167	0.122
Plaque laterality categories ("Neither" omitted)					
Unilateral	0.099	0.030	0.001	0.040 to 0.158	0.129
Bilateral	0.143	0.031	0.000	0.082 to 0.205	0.129

ApoA-1: Apolipoprotein A-1, ApoB: Apolipoprotein B, CIMT: carotid intima-media thickness, CI: confidence interval, eGFR: estimated glomerular filtration rate, LDL: low-density lipoprotein, SE: standard error

Table III: Multivariable models showing association with carotid intima-media thickness

Carotid intima-media thickness regression models						
Variable	Model 1		Model 2		Model 3	
	Beta (change in CIMT in mm)	SE	Beta (change in CIMT in mm)	SE	Beta (change in CIMT in mm)	SE
Age (years)	0.007***	0.001	0.007***	0.001	0.007***	0.001
LDL (mmol/l)	0.021*	0.012				
High ApoB:ApoA-1 ratio			0.043*	0.026		
ApoB/ApoA-1					0.067*	0.040
Constant	0.341***	0.069	0.408***	0.063	0.365***	0.069
Adjusted R ²	0.22		0.21		0.21	
CIMT regression models with outliers excluded						
Variable	Model 1		Model 2		Model 3	
	Beta	SE	Beta	Beta	SE	Beta
Age (years)	0.005***	0.001	0.005***	0.001	0.005***	0.001
LDL (mmol/l)	0.010	0.010				
High ApoB:ApoA-1 ratio			0.025	0.022		
ApoB/ApoA-1					0.054	0.033
Constant	0.458***	0.060	0.498***	0.054	0.463***	0.059
Adjusted R ²	0.18		0.17		0.17	

*** p-value < 0.01, ** p-value < 0.05, * p-value < 0

ApoA-1: Apolipoprotein A-1, ApoB: Apolipoprotein B, CIMT: carotid intima-media thickness, LDL: low-density lipoprotein, SE: standard error

model because of multicollinearity. None of the lipid parameters were statistically significant at a 5% level, although all had p-values < 0.10. However, the models all had p-values < 0.05. The model with the highest R-squared was the model with age and LDL cholesterol (22% of the variation in CIMT could be explained by these two variables), although it was very similar to the other models. Given the relatively small sample size of 185 individuals, outliers could influence the regression coefficients and R-squared considerably. Three outliers with high leverage were identified, and if the analyses were repeated with these excluded, the p-values for all the lipid parameters were > 0.01 (LDL: p-value = 0.29; high ApoB:ApoA-1 ratio: p-value = 0.26; ApoB:ApoA-1 ratio: p-value = 0.11) and the largest R-squared was reduced to 18%. Inverse serum creatinine became nonsignificant after adjusting for age.

Statin use could potentially be a confounder in the studied associations. Only 24% of patients were on a statin at the time of investigation and had probably only recently started. (The duration was not measured.) There was no association between statin use and CIMT [β -0.005 standard error (0.029), p-value = 0.87]. Statin use was also not related to LDL, ApoA-1 or the ApoA-1:ApoB ratio (data not shown).

If eGFR was used in the above models, instead of age (eGFR could not be tested by adjusting for age, as age is used to calculate eGFR), eGFR stayed significant (coefficient -0.002, p-value < 0.01) with very little change in the lipid coefficients, but the adjusted R-squared dropped to 6% in all three models. Albuminuria was not tested in the multivariate models, as it was nonsignificant in the univariate analysis.

Discussion

Given that CIMT has been identified as a surrogate marker for increased cardiovascular risk, it is important to determine which factors, if any, contribute to the CIMT in our local population. In this study of mainly black (87%) subjects, aged on average 60 years with type 2 diabetes mellitus of mean 10 years duration, we studied the factors that were found to be associated with CIMT in other studies.

As expected, age was the major determinant of CIMT. The other clinical and demographic variables that were significantly related showed only a weak relationship. Besides age, lipid parameters showed the strongest association of all the variables when combined in a multivariable model. However, none of the variables was statistically significant in a multivariate model. Outliers also changed coefficients and the R-squared significantly.

When the black patients in the Interheart Study were analysed separately, elevated ApoB:ApoA-1 ratio

(tertiles 2 and 3 vs. 1) showed an odds ratio of 3.43 (95% CI, 2.06-5.71) for acute myocardial infarction, with a population-attributable risk of 52%.³⁷ The Interstroke Study, with more than 300 participants from Africa, showed an odds ratio of 2.33 (95% CI, 1.80-3) for elevated ApoB:ApoA-1 ratio (tertile 3 to 1) regarding ischaemic stroke.³⁸ This highlights the importance of ApoB:ApoA-1 as a risk factor for both acute myocardial infarction and stroke. This is probably relevant for all population groups in South Africa.

Ethnic differences in the prevalence of subclinical atherosclerosis have been studied. As early as 1996, the Insulin Resistance Atherosclerosis Study found that black subjects had significantly greater common CIMT than non-Hispanic white subjects (865 vs. 808 μ m). This remained significant after adjusting for major cardiovascular disease risk factors and insulin sensitivity (864 vs. 823 μ m).³⁹

In the diabetic population of the Multi-Ethnic Study of Atherosclerosis (MESA),⁴⁰ the investigators found that there were no ethnic differences in CIMT, but there were differences in the coronary artery calcium scores. White subjects had higher scores than black subjects.

Closer to home, the Sympathetic Activity and Ambulatory Blood Pressure in Africans (SABPA) study⁴¹ that was carried out in the North West province of South Africa among black and white school teachers (mean age 45 years), found that black teachers had a higher CIMT (mean of near and far wall of 0.044, 95% CI: 0.024-0.064), a difference that was reduced to 0.023 (p-value = 0.082) after controlling for conventional and behavioural risk factors.

In our study, the urinary albumin:creatinine ratio was not associated with CIMT cross-sectionally. Approximately 90% of the study population had hypertension and the majority of these would be on an angiotensin-converting enzyme inhibitor. This could alter the relationship between albuminuria and CIMT when studied cross-sectionally. The eGFR was significantly associated with CIMT univariately, as well as multivariately. However, it seems that the major contribution was due to age.

Discrepancies between studies that have evaluated associations with CIMT can be due to the measurements of the CIMT used. For example, the Japanese study¹⁹ evaluated a similar group of patients and found that age (β 0.145, p-value = 0.047), sex (β -0.147, p-value = 0.054) and HDL cholesterol (β -0.145, p-value = 0.048) were important in a multivariate model that included LDL cholesterol particle size, glycated LDL cholesterol, as well as malondialdehyde-modified LDL. However, that study used the largest CIMT among the values for the right and left common carotid artery, carotid bulb and internal carotid artery as the outcome variable for each patient.

Lipid parameters were related to CIMT in our study population. However, this did not reach statistical significance in this relatively small sample. It highlights the fact that much larger studies would be required to show significant associations in our population.

The strength of our study is the fact that the CIMT measurements included multiple measurements at multiple angles carried out by sonographers, meeting quality standards for CIMT measurement. The fact that the study was a cross-sectional convenience sample of less than 200 patients is a weakness, but we are confident that no systematic bias in the association with CIMT could have occurred.

In conclusion, in the multivariable analyses of our study sample, we did not find that blood pressure or kidney function was related to CIMT. Besides age, the strongest associations were with the lipid parameters, but these were not statistically significant, and added very little to the variability of CIMT compared with age alone.

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