Atherosclerotic vascular disease and its correlates in stable black South African kidney transplant recipients

Stephen Olawale Oguntola¹
Muzamal Olamide Hassan²
Raquel Duarte³,*
Therese Dix-Peek³
Caroline Dickens³
Gbenga Olorunfemi⁴
Ahmed Vachiat⁵
Graham Paget¹
Pravin Manga⁵
Saraladevi Naicker¹,*

¹Department of Internal Medicine, Division of Nephrology, University of Witwatersrand, Johannesburg, South Africa; ²Department of Internal Medicine, Dialysis Unit, Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Nigeria; ³Department of Internal Medicine Laboratory, University of Witwatersrand, Johannesburg, South Africa; ⁴Department of Epidemiology and Biostatistics, School of Public Health, University of Witwatersrand, Johannesburg, South Africa; ⁵Department of Internal Medicine, Division of Cardiology, University of Witwatersrand, Johannesburg, South Africa

*These authors contributed equally to this work

Background: Despite remarkable improvement in renal function attributable to kidney transplantation, the burden of cardiovascular disease (CVD) among kidney transplant recipients (KTRs) remains high in the post-transplant period. Aggressive use of statins in KTRs may make lipoprotein ratios correlate better with atherosclerotic vascular disease (AsVD) when compared with traditional lipid profile parameters. We therefore evaluated the clinical and echocardiographic correlates of AsVD among non-diabetic, stable, black KTRs in South Africa.

Methods: This was a cross-sectional study of 41 adult (18–65 years), non-diabetic, stable KTRs and 41 age- and sex-matched healthy controls. An interviewer-administered questionnaire was used to obtain information on participants’ sociodemographic and cardiovascular risk factors. Anthropometric parameters were measured. Urine and blood samples were obtained and analyzed. Echocardiography was performed and carotid intima media thickness (CIMT) was assessed in both right and left carotid arteries. Spearman’s rank correlation and binary logistic regression were performed to determine the relationship between CVD risk factors and AsVD.

Results: AsVD was present in 46.3% of KTRs compared to 17.1% of healthy controls (p = 0.004). Left ventricular hypertrophy was present in 92.7% of the KTRs. There were statistically significant differences in waist–hip ratio, systolic blood pressure, mean arterial pressure, urine albumin–creatinine ratio, serum fibrinogen, serum creatinine, estimated glomerular filtration rate, left atrial diameter, left ventricular mass (LVM), and left ventricular mass index (LVMI) between KTRs and controls. A positive relationship was seen between CIMT and certain risk factors for CVD including LVM, LVMI, and mitral valve deceleration time, (p < 0.001). Castelli index 2 and lipoprotein combine index (LCI) showed positive correlation with CIMT. On multivariate analysis, increasing age and kidney transplant status were independent predictors of AsVD after controlling for other risk factors.

Conclusion: AsVD was common among KTRs. Older age and kidney transplant status independently predicted AsVD. Castelli index 2 and LCI correlated with AsVD better than serum lipid parameters.

Keywords: carotid intima media thickness, lipoprotein ratios, Castelli index 2, lipoprotein combine index, left ventricular mass index

Introduction

Kidney transplantation offers a greater survival benefit compared to dialytic therapy in end-stage kidney disease (ESKD) patients;¹ however, a high prevalence of cardiovascular disease (CVD) among kidney transplant recipients (KTRs) predisposes them to increased mortality in comparison to healthy controls.²³ Risk factors for vascular disease identified among KTRs in an American study included age, sex, cigarette smoking,
pre-transplant splenectomy, and serum albumin. Tradition-
ally, a favorable lipid profile among black Africans was iden-
tified as the reason for a lower prevalence of atherosclerotic
vascular disease (AsVD) and ischemic heart disease, despite
the presence of other cardiovascular risk factors. However,
a rise has been reported in the prevalence of dyslipidemia
and ischemic heart disease in the urban black population of
South Africa. This trend has been attributed to increasing
urbanization, changes in diet, and a reduction in physical
activity. Additionally, the high prevalence of both traditional
and chronic kidney disease (CKD)-related cardiovascular risk
factors among ESKD patients has contributed to the high
risk of AsVD among this group of patients. A case–control
study among black South African ESKD patients reported a
higher prevalence of carotid plaques among ESKD patients
on maintenance hemodialysis (38.1%) when compared with
controls (7.9%). Furthermore, Muhammad et al found
left ventricular hypertrophy (LVH) to be prevalent among
KTRs and also reported that a longer duration on dialysis,
cigarette smoking, higher cumulative steroid dose, increased
carotid intima media thickness (CIMT), and increased waist
circumference predicted the presence of LVH. In view of the
aggressive use of lipid-lowering medications in CKD and
post-kidney transplantation, use of conventional lipid profiles
for cardiovascular risk assessment in this group of patients
may not provide the whole picture. Lipoprotein ratios may
correlate better with AsVD than lipid profile parameters. The
discriminatory and predictive power of total cholesterol (TC)/
high-density lipoprotein (HDL) was found to be superior
to either TC or HDL. Lipoprotein ratios have been shown
to be superior to conventional lipid profiles in predicting
coronary heart disease. Furthermore, sociodemographic
characteristics and possibly genetic variations may impact
the cardiovascular risk among KTRs in our environment.
Although some studies have evaluated CVD among black
ESKD, maintenance dialysis, and renal transplant patients,
a significant knowledge gap of the risk factors for AsVD
among stable, black KTRs in the absence of diabetes and
inflammatory conditions still exists.

In view of the paucity of knowledge about AsVD among
black South African KTRs, we evaluated the relationship of
dyslipidemia and lipoprotein ratios to AsVD among non-
diabetic, stable, black KTRs.

Methods
This was a comparative cross-sectional study of 41 adult (age
18–65 years) non-diabetic, stable KTRs and 41 age- and sex-
matched healthy controls at a large urban public hospital in
South Africa from January 2, 2017 to August 31, 2017. The
study was approved by the Human Research Ethics Com-
mittee, University of Witwatersrand, Johannesburg, South
Africa (Study number 160614). All participants provided
signed informed consent before enrollment in the study. An
interviewer-administered questionnaire was used to obtain
information on the participants’ sociodemographic and car-
diovascular risk factors.

Waist and hip circumferences were measured with
patients in an erect position and waist–hip ratios (WHR)
calculated. Body mass index (BMI) was calculated using
the formula mass/height², while body surface area was cal-
culated using the Mosteller formula. Serum fibrinogen was
determined using STA-R Max (Stago, Asnières-sur-Seine,
France). A serum lipogram (TC, low-density lipoprotein
[LDL], triglyceride [TG], HDL) was determined by an enzy-
ic colorimetric method using the Cobas 8000 modular
analyzer series, module c701 analyzer (Hoffman-La Roche
Ltd., Basel, Switzerland). Lipoprotein ratios were calculated
as follows: atherogenic index of plasma = Log (TG/HDL);

\[
\frac{1}{\text{LDL/HDL}} \quad \text{LDL/HDL} = \frac{\text{TC/HDL}}{\text{non-HDL/HDLD}}
\]

CIMT measurements in accordance with the guidelines of
the American Society of Echocardiography, using a Philips
iE33 echocardiography machine (Philips, Amsterdam, the
Netherlands). CIMT was assessed using the vascular probe
of the echocardiography machine, Philips IE33 (SS-1 probe)
by focusing on the far wall of the common carotid artery, 1
cm proximal to the dilatation of the carotid bulb along the
long axis of the artery. Automatic echo-generated measure-
ments with percentage quality of 95% were recorded. The
procedure was performed on both the left and right carotid
arteries and the average used in analysis.

Data analysis
Stata version 13.1 (StataCorp LP, College Station, TX, USA)
was used for statistical analysis. Categorical variables were
expressed as frequencies and percentages and compared
using the chi-square test. A Shapiro–Wilk test of normality
was performed on all continuous variables and normally
distributed data were presented as mean ± SD, while
non-normally distributed data were presented as median and interquartile range (IQR). Comparisons were performed between KTRs and controls, and between participants who had AsVD and those who did not, using the Student’s t-test for normally distributed data and the Wilcoxon rank-sum test for non-normally distributed data.

Spearman’s correlation was used to determine the relationship between CIMT and cardiovascular risk factors among KTRs and controls. Multivariate regression analysis was performed to determine the relationship and contribution of cardiovascular risk factors to AsVD. Significance was taken as \( p<0.05 \). Post-regression analysis was performed to determine the goodness-of-fit of the final model.

## Results

The median age was 39 years (IQR: 30–52) among KTRs while the median age among the control group was 41 years (IQR: 29–48), as shown in Table 1. The most common causes of ESKD in the KTR population were hypertension-attributed CKD and glomerulonephritis (both \( n = 19, 46.3\% \)).

All the KTRs were on calcineurin inhibitor (CNI)-based immunosuppressive therapy (with more than 90% on Tacrolimus while \(<10\%\) were on cyclosporine), antimetabolites (30 [73.2\%] were on mycophenolate mofetil, five [12.2\%] were on mycophenolic acid, four [9.8\%] were on azathioprine, and two [4.9\%] were on Leflunomide), and 5 mg maintenance prednisone daily. The majority (\( n = 38/41, 92.7\% \)) of the KTRs had received deceased donor organs while three (7.3\%) had related living donor transplantation. The median post-transplant follow-up duration was 4 years (IQR: 1–7) while median pre-transplant dialysis duration was 5 years (IQR: 4–6). LVH was present in 34 (82.9\%) of the KTRs; 15/17 (88.2\%) of KTRs with GFR <60 mL/min/173 m² and in 13/18 (72.2\%) KTRs with elevated blood pressure. Among the KTRs, 24 (58.5\%) had concentric hypertrophy (relative wall thickness [RWT] > 0.42 and left ventricular mass index [LVMI] >95 g/m² for females or >115 g/m² for males), ten (24.4\%) had eccentric hypertrophy (RWT \(<0.42 \) and LVMI >95 g/m² for females or >115 g/m² for males), five (12.2\%) had concentric remodeling (RWT >0.42 and LVMI \(<95 \text{ g/m² for females or } \leq 115 \text{ g/m² for males}), and two (4.9\%) had normal geometry. Using the combination of increased CIMT values (>0.55 mm) and the presence of plaques, AsVD was present in 19 (46.3\%) KTRs compared to seven (17.1\%) healthy controls, (\( p=0.004 \)). CIMT was significantly increased among the KTRs compared to the controls (\( p=0.021 \)). As shown in Table 2, significant differences were seen between other echocardiographic measurements when KTRs were compared to controls. There was no association between CNI agents and AsVD, (\( \chi^2 = 1.46, p = 0.321 \)).

There was a statistically significant difference in Castelli 1 and 2 indices, Al, non-HDL, and LCI in those with AsVD compared to those without AsVD (Table 3). There were no statistically significant differences in the serum levels of TC, TG, LDL, and HDL. Spearman’s correlation between CIMT and risk factors for CVD among KTRs revealed a positive relationship with LVM (\( r = 0.52, p < 0.001 \)), LVH (\( r = 0.53, p < 0.001 \)), LAD (\( r = 0.43, p = 0.007 \)), age (\( r = 0.43, p = 0.005 \)), and WHR (\( r = 0.39, p = 0.012 \)) as shown in Table 4. Of the lipid profile parameters and lipoprotein ratios in KTRs, only Castelli 2 index and LCI showed correlation with CIMT.

The multivariable model of the predictors of AsVD showed that KTR status confers an 11-fold risk of developing AsVD (OR = 11.22, 95% CI = 1.82–68.93, \( p = 0.009 \)); Table 5. The odds of developing AsVD was 17 times higher in subjects \( \geq 40 \) years (\( p = 0.001 \)). Age and KTR status were independent predictors of AsVD after correcting for WHR,
Table 2: Comparison of cardiovascular risk factors between kidney transplant recipients and controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>KTR (n = 41)</th>
<th>Control (n = 41)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39 (30–52)</td>
<td>41 (29–48)</td>
<td>0.824*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7 (23.1–28.5)</td>
<td>28.7 (22.9–31.2)</td>
<td>0.081*</td>
</tr>
<tr>
<td>WHR</td>
<td>0.89±0.07</td>
<td>0.85±0.06</td>
<td>0.002*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>139.7±15.8</td>
<td>125.4±11.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>106.9±13.8</td>
<td>94.6±11.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.46 (3.93–4.93)</td>
<td>4.27 (3.71–4.70)</td>
<td>0.330*</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.63 (2.15–3.08)</td>
<td>2.59 (2.08–3.17)</td>
<td>0.777*</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.31 (1.06–1.92)</td>
<td>1.25 (0.80–1.53)</td>
<td>0.399*</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.29 (1.05–1.47)</td>
<td>1.15 (0.98–1.54)</td>
<td>0.467*</td>
</tr>
<tr>
<td>Urine-ACR (mg/mmol)</td>
<td>4.60 (1.20–16.2)</td>
<td>0.40 (0.20–0.80)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.00 (2.60–3.5)</td>
<td>2.50 (2.20–3.20)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Scr (µmol/L)</td>
<td>123 (91–152)</td>
<td>80 (63–89)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>71 (49–85)</td>
<td>113 (99–124)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>35.9 (32.3–34.6)</td>
<td>31.02 (29.0–32.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>CIMT (mm)</td>
<td>0.60 (0.51–0.66)</td>
<td>0.53 (0.47–0.60)</td>
<td>0.021*</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>219 (187–284)</td>
<td>174 (142–226)</td>
<td>0.001*</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>130.0 (108.4–165.2)</td>
<td>101.1 (73.8–115.7)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Notes: *Mean ± SD, Student’s t-test; median (interquartile range), Wilcoxon rank-sum test.

Abbreviations: KTR, kidney transplant recipient; AsVD, atherosclerotic vascular disease; BMI, body mass index; WHR, waist–hip ratio; SBP, systolic blood pressure; MAP, mean arterial pressure; TC, total cholesterol; LDL, low-density lipoprotein; urine-ACR, urine albumin–creatinine ratio; eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; LVM, left ventricular mass; LVMi, left ventricular mass index.

Table 3: Comparison between participants with atherosclerotic vascular disease and without it.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AsVD present (n = 62)</th>
<th>AsVD absent (n = 66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.0 (41.0–55.0)</td>
<td>32.5 (27.0–44.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>WHR</td>
<td>0.91 (0.86–0.93)</td>
<td>0.86 (0.83–0.90)</td>
<td>0.028*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5 (24.0–31.2)</td>
<td>27.1 (21.5–30.0)</td>
<td>0.273*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>139.2 (132.6–145.9)</td>
<td>140.1 (132.3–147.0)</td>
<td>0.855*</td>
</tr>
<tr>
<td>AIP</td>
<td>0.03 (–0.03–0.11)</td>
<td>0.02 (–0.08–0.12)</td>
<td>0.729*</td>
</tr>
<tr>
<td>Castelli 1</td>
<td>4.1 (3.1–4.9)</td>
<td>3.1 (2.5–4.1)</td>
<td>0.033*</td>
</tr>
<tr>
<td>Castelli 2</td>
<td>2.5 (1.6–3.2)</td>
<td>1.8 (1.3–2.6)</td>
<td>0.048*</td>
</tr>
<tr>
<td>LCI</td>
<td>15.4 (10.1–18.9)</td>
<td>8.7 (4.4–19.6)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Non-HDL</td>
<td>3.4 (2.8–4.0)</td>
<td>2.9 (2.3–3.5)</td>
<td>0.019*</td>
</tr>
<tr>
<td>AI</td>
<td>3.0 (2.1–3.9)</td>
<td>2.1 (1.5–3.2)</td>
<td>0.034*</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.5 (4.1–5.1)</td>
<td>4.3 (3.5–4.8)</td>
<td>0.071*</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.3 (1.1–2.1)</td>
<td>1.1 (0.8–1.7)</td>
<td>0.139*</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.7 (2.2–3.3)</td>
<td>2.6 (2.0–2.9)</td>
<td>0.087*</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.1 (0.9–1.4)</td>
<td>1.3 (1.1–1.6)</td>
<td>0.163*</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.0 (2.6–3.5)</td>
<td>2.5 (2.2–3.2)</td>
<td>0.041*</td>
</tr>
<tr>
<td>Urine-ACR (mg/mmol)</td>
<td>2.8 (0.3–8.1)</td>
<td>0.2 (0.3–6.2)</td>
<td>0.056*</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>86.5 (54.0–117)</td>
<td>97.5 (70.5–116.0)</td>
<td>0.386*</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>37.5 (32.0–40.0)</td>
<td>32.0 (29.0–35.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LVM (g/m²)</td>
<td>135.1 (118.2–168.2)</td>
<td>103.9 (81.6–123.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Dec. time (ms)</td>
<td>172.5 (155.0–201.0)</td>
<td>148.0 (129.5–171.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>EF (%)</td>
<td>73.0 (64.0–79.0)</td>
<td>68.0 (62.5–74.0)</td>
<td>0.229*</td>
</tr>
</tbody>
</table>

Notes: *Mean ± SD, Student’s t-test; median (interquartile range), Wilcoxon rank-sum test.

Abbreviations: KTR, kidney transplant recipient; AsVD, atherosclerotic vascular disease; BMI, body mass index; SBP, systolic blood pressure; AIP, atherogenic index of plasma; LCI, lipoprotein combine index; HDL, high-density lipoprotein; AI, atherogenic index; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; urine-ACR, urine albumin–creatinine test; eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; LVM, left ventricular mass index; Dec. time, mitral valve deceleration time; EF, ejection fraction.

proteinuria, GFR, Castelli index 2, and LVH. The goodness-of-fit of the model was assessed by the Hosmer–Lemeshow test (p = 0.319). Binary logistic regression analysis among KTRs showed that age >40 years independently predicted AsVD after adjusting for post-transplant follow-up duration, duration of dialysis and LVH, Table 6.
Table 4 Correlation of carotid intima media thickness to risk factors for cardiovascular disease among kidney transplant recipients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>KTR (n = 41)</th>
<th>Controls (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rho</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.42</td>
<td>0.006*</td>
</tr>
<tr>
<td>WHR</td>
<td>0.39</td>
<td>0.017*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.17</td>
<td>0.296</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>0.29</td>
<td>0.071</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>0.20</td>
<td>0.203</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>0.30</td>
<td>0.050</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>0.09</td>
<td>0.566</td>
</tr>
<tr>
<td>Castelli 1</td>
<td>0.27</td>
<td>0.082</td>
</tr>
<tr>
<td>Castelli 2</td>
<td>0.33</td>
<td>0.035*</td>
</tr>
<tr>
<td>AIP</td>
<td>0.13</td>
<td>0.408</td>
</tr>
<tr>
<td>Non-HDL</td>
<td>0.29</td>
<td>0.071</td>
</tr>
<tr>
<td>Atherogenic index</td>
<td>0.28</td>
<td>0.082</td>
</tr>
<tr>
<td>LCI</td>
<td>0.31</td>
<td>0.047*</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.32</td>
<td>0.044*</td>
</tr>
<tr>
<td>FS (%)</td>
<td>0.27</td>
<td>0.090</td>
</tr>
<tr>
<td>E/e'</td>
<td>0.21</td>
<td>0.180</td>
</tr>
<tr>
<td>Dec. time (ms)</td>
<td>0.59</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>0.50</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>0.50</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>0.42</td>
<td>0.007*</td>
</tr>
</tbody>
</table>

Note: *Statistically significant, p<0.05.
Abbreviations: E/e', ratio of transmitral doppler early filling velocity to tissue doppler early diastolic mitral annular velocity; KTR, kidney transplant recipient; WHR, waist-hip ratios; BMI, body mass index; eGFR, estimated glomerular filtration rate; TC, total cholesterol; LDL, low-density lipoprotein; TG, triglycerides; AIP, atherogenic index of plasma; HDL, high-density lipoprotein; LCI, lipoprotein combine index; EF, ejection fraction; FS, fractional shortening; Dec. time, mitral valve deceleration time; LVM, left ventricular mass; LVMi, left ventricular mass index; LAD, left atrial diameter.

Table 5 Logistic regression showing relationship of atherosclerotic vascular disease to risk factors of cardiovascular disease

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>17.12</td>
<td>3.36–87.12</td>
<td>0.001*</td>
</tr>
<tr>
<td>WHR</td>
<td>0.56</td>
<td>0.14–2.17</td>
<td>0.401</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>0.34</td>
<td>0.67–1.73</td>
<td>0.193</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1.29</td>
<td>0.23–5.20</td>
<td>0.720</td>
</tr>
<tr>
<td>Kidney transplant status</td>
<td>11.22</td>
<td>1.82–68.93</td>
<td>0.009*</td>
</tr>
<tr>
<td>Castelli index 2</td>
<td>1.95</td>
<td>0.57–6.73</td>
<td>0.288</td>
</tr>
<tr>
<td>LVH (g/m²)</td>
<td>2.49</td>
<td>0.42–14.60</td>
<td>0.312</td>
</tr>
</tbody>
</table>

Note: *Statistically significant, p<0.05.
Abbreviations: WHR, waist-hip ratios; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy.

Discussion

AsVd was significantly more prevalent among KTRs compared to controls in our study, with nearly half of the KTRs having AsVd. This is comparable with findings from previous studies. Basiratnia et al demonstrated a higher mean CIMT in KTRs compared to healthy controls. Similarly, Cader et al found a significantly higher prevalence of increased CIMT among their cohort of KTRs. Although the control group in our study and the study by Basiratnia et al were similar, in the study by Cader et al the controls were CKD stage and cardiovascular risk matched. Prevalence of AsVd in our study (46.3%) is very similar to that reported in a previous study by Japichino et al (46.5%). The higher prevalence of AsVd (66.7%) reported by Cader et al could be due to visualization of carotid plaques and measurement of CIMT at the carotid bulb, and also because of differences in participants’ profiles with diabetes mellitus accounting for one third of subjects recruited in their study; we had excluded patients with diabetes mellitus and current smokers. The high prevalence of AsVd in our study can be explained by the significant differences in the levels of some established cardiovascular risk factors such as blood pressure, WHR, proteinuria, GFR, LVH, and LAD in KTRs compared to controls.

We found a strong association between AsVd and cardiovascular risk factors. Age, WHR, Castelli indices 1 and 2, non-HDL, A1, LCI, serum fibrinogen levels, LAD, LVH, and mitral valve deceleration time were also significantly associated with the presence of AsVd in our study, comparable to results from previous studies. Kolonko et al found age, pre-transplant diabetes, LVH, and CVD to be related to CIMT, which is similar to our findings, despite the exclusion of diabetic KTRs from our study based on the known association between diabetes, dyslipidemia, and atherosclerosis. Serum fibrinogen has been shown to increase inflammatory and atherosclerotic conditions, possibly through the elaboration of inflammatory cytokines by macrophages involved in atherosclerosis and subsequent stimulation of fibrinogen production by these cytokines. In our study population, serum fibrinogen was significantly higher among KTRs compared to controls and also significantly higher among participants who had AsVd compared to those without AsVd. AsVd is currently viewed as an inflammatory disease and serum levels of fibrinogen have been influenced by several risk factors of CVD such as hypertension, diabetes, and inflammation.
Among a cohort of ESKD patients on chronic hemodialysis, serum fibrinogen was found to be higher among patients with fatal and non-fatal cardiovascular events compared to event-free patients. Our study, which demonstrates an association between AsVD and LVH is supported by reports from an earlier study which described LVH as both a CVD and a risk factor for CVD.

Our study found that age, WHR, Castelli 2, LAD, LVM, and LVI had positive correlations with CIMT; the association between increased CIMT and age had been described in a previous study. Also, advancing age has been associated with diminished nitric oxide-mediated vasodilatation and reduction in total nitric production, resulting in endothelial dysfunction. Increasing age has also been associated with other risk factors for AsVD such as diabetes, hypertension, and vascular calcification. LVH is an important predictor of all-cause mortality among KTRs. Our study showed a negative correlation between LVH and renal function ($r = -0.25$, $p = 0.02$), consistent with earlier studies in pre-dialysis CKD patients and KTRs. An increased WHR has been associated with cardiovascular events among CKD patients; the finding of a positive correlation between WHR and CIMT in our study is probably due to the use of steroids by the KTRs but may also be explained by the fact that restoration of renal function after kidney transplantation reduces CKD-related inflammation and malnutrition, enhancing appetite and weight gain.

In our study population, among all the lipid profile and lipoprotein indices analyzed, only Castelli 2 index and LCI correlated positively with CIMT. This finding could be due to the aggressive treatment of dyslipidemia with statins in our patients. Sub-analysis within the KTR group showed that Castelli 2 index retained its positive correlation with CIMT ($r = 0.33$ $p = 0.035$) while LDL showed a marginally significant correlation. There was no correlation between blood pressure and CIMT, possibly due to the aggressive blood pressure treatment in our KTRs who had a median blood pressure of 139.7/89.5 mmHg.

Age and KTR status were independent predictors of AsVD even after correcting for WHR, proteinuria, GFR, Castelli index 2, and LVH (Table 4). Among KTRs, only age >40 years predicted AsVD even when adjusted for LVH, duration of dialysis and post-transplant duration. Increasing age has been demonstrated to be an important predictor of vascular injury and atherosclerosis has been shown to be associated with changes in CIMT early in the post-kidney transplant period.

This study excluded patients with diabetes mellitus, connective tissue diseases and inflammatory disorders, acute and chronic infections, and smokers. Furthermore, only stable, black KTRs were recruited. This could have contributed to the lower prevalence of AsVD seen in this study compared to the other studies alluded to in the discussion.

In conclusion, AsVD is common among KTRs. Strong correlations exist between CIMT and age, WHR, LVH, LAD, ejection fraction, and mitral valve deceleration time. Among the KTRs’ lipoprotein indices, namely Castelli index 2 and LCI, showed a better correlation with CIMT than conventional lipid profile parameters. Age and KTR status were independent predictors of AsVD. The findings of this study suggest that serum fibrinogen, Castelli index 2, and LCI may be important surrogate markers of atherosclerosis in KTRs. It is recommended that the levels of these markers be determined before renal transplantation and monitored in the post-transplant period. In addition, we also recommend more aggressive surveillance for AsVD among KTRs older than 40 years of age.

Acknowledgments

This work was made possible by the ISN fellowship granted to Dr SO Oguntola to study at the Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa, and forms part of his PhD thesis to be submitted to the University of Witwatersrand. This study was financed through supervisors’ (S Naicker and R Duarte) research grants from the National Research Foundation of South Africa.

The authors wish to express their appreciation to Jamie Leigh-Hayes for her assistance during data collection.

Disclosure

The authors report no conflicts of interest in this work.

References

16. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18(12):1440–1463.