Tropical Journal of Nephrology Vol. 16 Nos. 1 and 2, June and December, 2021 17 - 26

Prevalence, Correlates and Predictors of Carotid Intima Media Thickness among Nigerian Chronic Kidney Disease Patients

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ABSTRACT

Background: Chronic kidney disease (CKD) is a major public health burden with global increase in prevalence, morbidity and mortality. Cardiovascular disease is the major cause of morbidity and early mortality in chronic kidney disease patients. Carotid intima media thickness (CIMT) correlates with future cardiovascular and cerebrovascular events and measurement of CIMT has been suggested as a suitable, valuable and evidence-based tool to predict and evaluate cardiovascular risk. The study assessed the prevalence, correlates and predictors of CIMT among CKD patients attending Usmanu Danfodiyo University Teaching Hospital Sokoto.

Methods: The study was cross-sectional in design. A total of 80 CKD patients and 80 healthy control subjects were enrolled. Socio-demographic, clinical and laboratory data were obtained using a structured proforma. CIMT was measured using 7.5MHZ linear probe in B mode regime and dynamic range set at 60db. An average of six measurements; 3 from each side of the carotid was taken as the final CIMT. Clinical and laboratory data were collected using a structured proforma. Data was analysed using SPSS version 25.

Results: The prevalence of increased CIMT among CKD patients was 63.7% and a statistically significant difference in mean CIMT between the CKD group 0.96±0.15mm and control 0.5±0.15mm, p-value<0.001. The mean CIMT increased across the stage of CKD with a statistically significant difference, p-value<0.01. There was no statistically significant difference in CIMT across aetiology of CKD. A positive correlation existed between increased CIMT measurements with age, serum creatinine, intact parathyroid hormone and high sensitivity C-reactive protein (hsCRP) but a strong negative correlation was observed between CIMT and eGFR. Using multiple linear regression, the strongest predictor of CIMT was found to be hsCRP.

Conclusion: There is a significantly higher CIMT measurements in CKD patients compared to age and gender matched controls.

INTRODUCTION

Chronic kidney disease (CKD) is a major public health burden with global increase in prevalence, morbidity and mortality [1]. It is estimated recently that kidney disease contributes to more deaths than the four main non-communicable diseases (NCDs) targeted by the current NCDs action plan [2].

The prevalence of CKD is 15.8% in the general population in Africa with a higher prevalence in sub-Saharan Africa [3]. The crude prevalence rate of kidney damage in Nigeria was found to be 23.47% and renal diseases constitute 15.4% of all medical admissions [4,5]. The prevalence of CKD in Africa has increased due to increasing cardiovascular disease burden [6]. This demonstrates a relationship between cardiovascular diseases and chronic kidney disease.

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Cardiovascular disease is the major cause of morbidity and early mortality in chronic kidney disease [7]. The process of cardiovascular disease in CKD patients is thought to commence early even before commencement of renal replacement therapy [8]. More than half of pre-dialysis patients were found to have left ventricular hypertrophy in a study in Uganda [9]. Despite regular haemodialysis and improvement in dialysis technology, mortality rate of end stage renal disease was above 50% at 1 year and more than half are related to cardiovascular disease and CKD is regarded as a cardiovascular risk equivalent in most current guidelines [10,11].

Chronic kidney disease is a key factor in the development and acceleration of atherosclerosis, ischaemic vascular disease and cardiovascular death [11]. Atherosclerosis is a systemic disease; carotid and coronary vessels are at comparable risk for developing pathologic changes. For this reason, increase in the thickness of the intima-media layers of carotid arteries can be a harbinger of coronary atherosclerosis and also a prognostic factor for cardiovascular accidents [12]. The visualized lesions in the common carotid artery correlate with atherosclerosis in major vessels of other parts of the body. Moreover, increased carotid artery intima thickness correlates with future cardiovascular and cerebrovascular events [13]. Therefore, measurement of CIMT has been suggested as a suitable, valuable and evidence-based tool to evaluate and predict cardiovascular risk [14]. This study aims to investigate the prevalence of CIMT and to determine the contributions of other cardiovascular risk factors to the severity of CIMT in stage 3-5 CKD patients attending Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto.

MATERIALS AND METHODS

This cross-sectional study was carried out in the Nephrology Unit of UDUTH, Sokoto. The study population included 80 staged 3-5 CKD patients and 80 age and gender matched apparently healthy controls. The minimum sample size for this study to allow for a meaningful statistically significant analysis of result was obtained using the estimator for a comparative study [15]. Patients who fulfilled the inclusion criteria were recruited randomly from the medical outpatient department, wards and dialysis centre after obtaining an informed consent while the age and gender matched controls without diabetes, hypertension or proteinuria were selected from the community. Patients with any form of malignancy, neck trauma or on anti-lipid drugs were excluded from the study.

CKD was defined in this study as abnormalities of kidney structure or function, present for >3 months, with implications for health [16]. CKD was also staged based on eGFR determined using the CKD-EPI formular [16]. Demographic, clinical and laboratory data were collected using a structured open ended proforma. The clinical indices measured were height, weight, body mass index (BMI), waist circumference and blood pressure while the laboratory parameters measured were serum creatinine, lipid profile, haemoglobin, fasting blood glucose, urinalysis, serum calcium, phosphate, calcium phosphate product, serum intact parathyroid hormone and high sensitivity c-reactive protein. All participants had an electrocardiogram done to determine the presence of left ventricular hypertrophy.

Carotid intima media thickness measurement was carried out by a consultant radiologist. Standard procedure provided by the American Society of Echocardiography was adopted [17]. The intima-media thickness (IMT) of both carotid arteries were assessed using a high-resolution ultrasound machine Mindray SSD 5000 using a 7.5MHz linear probe in B mode regime. IMT was defined as a low-level echo grey band that does not project into the arterial lumen and was measured at the diastolic phase as the distance between the leading edge of the first and second echogenic lines. CIMT was measured on the longitudinal views of the far wall of the distal segment of the common carotid artery, the carotid bifurcation, and the initial tract of the internal carotid artery on both sides (three measurements on each side) in a plaque-free arterial segment. To increase validity and encourage reproducibility, dynamic range was set at 60 decibels [18]. Each measurement was an average of six measurements and all measurements were done by a single experienced radiologist. Normal value for CIMT was set at <0.9mm [11].

Statistics

Data from the proforma were recorded and analysed using IBM Statistical Package for Social Sciences (SPSS) version 25. Categorical data such as sex, ethnicity, educational status and aetiology of CKD

were summarized as frequencies and proportions (95% CI). Continuous data such as age, blood pressure, eGFR, iPTH, hsCRP and CIMT values were presented as means ± standard deviation. Chi-square and Fisher's exact tests were used to compare categorical variables such as sex, marital status, level of education, ethnicity, occupation, smoking, proteinuria and LVH in CKD group and non-CKD group.

Independent t test and/or Mann-Whitney U test was used to compare means and medians of continuous variables such as blood pressure, eGFR, haemoglobin, blood sugar, iPTH, hsCRP and CIMT values between CKD patients and control. Level of significance was set at $p \leq 0.05$. Pearson's correlation and/or Spearman rank correlation was used to investigate the linear relationship between CIMT and other continuous variables.

Point Biserial Correlation was used to determine if any relationship exist between CIMT and categorical CVD risk factors. Factors found to be significant in bivariate analysis were subjected to multivariate linear regression model to determine the predictors of CIMT. The regression analysis was presented in tables with confidence interval and their p- values. Level of significance (α) was set at 0.05.

RESULTS

A total of 160 subjects were recruited consisting of 80 chronic kidney disease patients, stages 3 to 5; and 80 healthy control subjects. However, 17 of the healthy control subjects were found to have Systolic Hypertension, 5 have diastolic blood pressure above cut off, 16 have significant proteinuria on dipstick and 2 have Fasting Blood Sugar above cut-off making a total of 40 of the healthy controls not suitable as controls and thus excluded from further analysis.

Table 1: Clinical and laboratory characteristics of the CKD group in comparison to control.

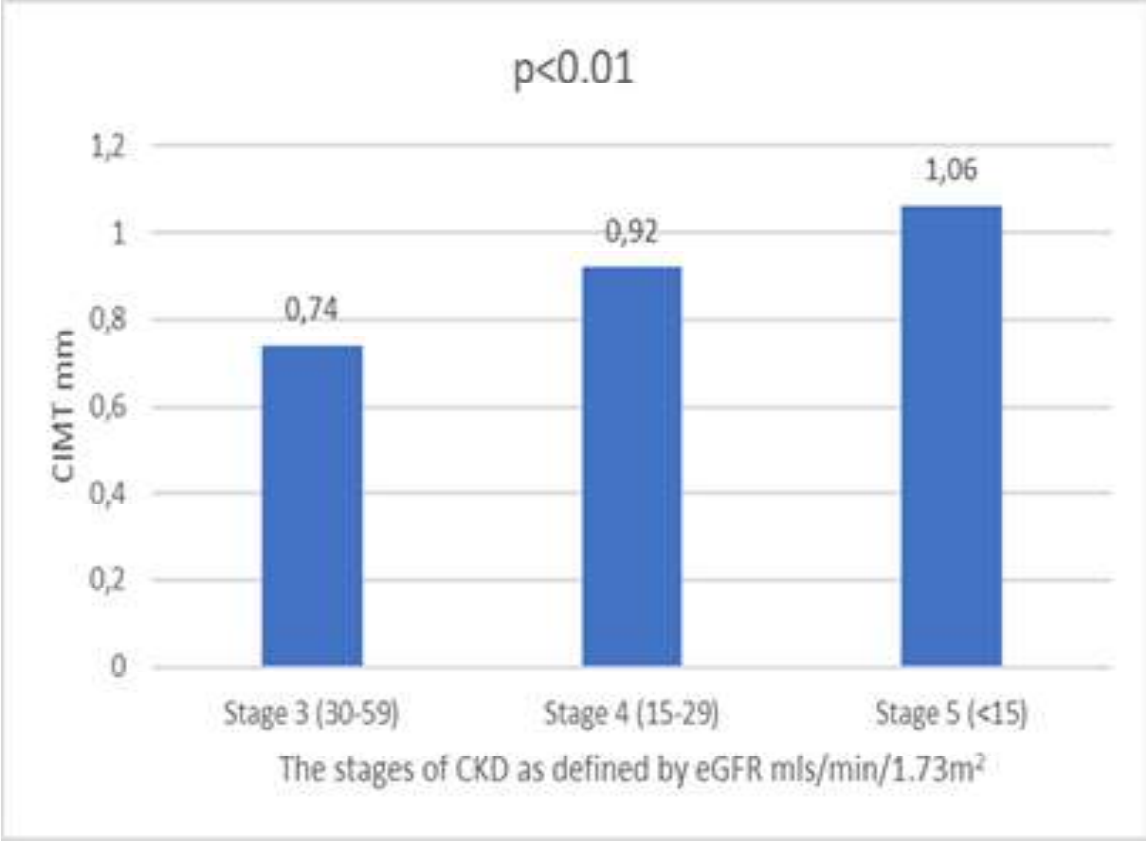
PARAMETER		CKD	CONTROL	P-VALUE
Duration of CKD (months)	Mean ± SD	8±10.7		
Systolic BP (mmHg)	Mean ± SD	155 ± 27.81	121.90±11.36	**<0.01**
Diastolic BP (mmHg)	Mean ± SD	97 ± 22.18	75.08±7.12	**<0.01**
Weight (Kg)	Mean ± SD	65.29 ± 11.11	63.60±9.50	**<0.01**
BMI (Kg/m^2)	Mean ± SD	23.40 ± 3.86	22.95±3.49	**<0.01**
Waist Circumference (cm)	Mean ± SD	88.42 ± 10.14	83.50±8.00	**<0.01**
Serum Creatinine (mg/dL)	Mean ± SD	5.35 ± 3.07	0.98±0.29	**<0.01**
eGFR (ml/min/1.73m^2)	Mean ± SD	17.30 ± 11.96	98.38±29.15	**<0.01**
Calcium (mg/dL)	Mean ± SD	1.73 ± 0.85	2.07± 0.34	**<0.01**
Phosphate (mg/dL)	Mean ± SD	1.45 ± 0.77	1.40± 0.26	**<0.01**
Calcium phosphate product (mg^2/dl^2)	Mean ± SD	31.46 ± 21.01	35.37±8.35	**<0.01**
Haemoglobin (g/dL)	Mean ± SD	8.62 ± 2.11	12.59±1.05	**<0.01**
Fasting blood sugar (mmol/L)	Mean ± SD	8.10 ± 2.79	4.47±0.90	**<0.01**
Proteinuria(dipstick)	Present	69 (86.2%)	0(0%)	**<0.01**
	Absent	11 (13.8%)	40(100%)	
Total Cholesterol (mg/dL)	Mean ± SD	172.25±60.45	142.63±35.22	**<0.01**
LDL cholesterol (mg/dL)	Mean ± SD	98.63 ±49.97	77.63±22.83	**<0.01**
Triglyceride (mg/dL)	Mean ± SD	163.31±73.77	143.25±43.34	**<0.01**
HDL cholesterol (mg/dL)	Mean ± SD	45.94±18.37	58.58±22.41	**0.02**
Intact Parathyroid hormone (pg/mL)	Mean ± SD	119.10±62.75	80.00±68.1	**<0.01**
High sensitivity CRP (mg/L)	Mean ± SD	16.90±6.64	9.96±15.22	**<0.01**
Left ventricular Hypertrophy	Present	43 (53.8%)	2 (5%)	**<0.01**
Sokolow-Lyon criteria >35mm	Absent	37 (46.3%)	38 (95%)	
Average CIMT (mm)	Mean ± SD	0.96 ±0.15	0.49 ± 0.11	**<0.01**

The mean age of the CKD subjects was 50.80 ± 15.09 years, with a male to female ratio of

1.8:1 while that of the control subjects was 49.63 ± 12.32 with a male to female ratio of 1.9:1. No statistically significant difference existed for age, sex and ethnicity.

Relationship between aetiology of CKD and CIMT
The mean CIMT in the CKD group as 0.96 ± 0.15mm and that of the control group as 0.49 ± 0.11mm. A statistically significant difference in CIMT measurement existed between the CKD group and control (P<0.01)). The percentage distribution of the aetiology of CKD from the study was CGN constituting 31.25% and ADPKD 3.75%. Diabetic nephropathy and hypertensive nephropathy each constituted 26.25%. The mean CIMT measurement in patients with DM nephropathy was higher (1.001±0.124) as against the other aetiologies of CKD but this did not reach statistically significant level (F=1503, p-value= 0.21) suggesting that the aetiology of the CKD may be an important key determinant of CIMT if more DM nephropathy CKD patients are recruited into the study.

Relationship between CIMT and CKD stage
The bar chart shows the mean CIMT measurements across the stages of CKD (stage 3-5) in the CKD group. The percentage distributions of the stages of CKD in the study were: stage 3(15%), stage 4 (33.8%) and stage 5 (51.2%). The mean CIMT increased with increased stage of CKD and a statistically significant difference existed between stages of CKD and CIMT measurements using analysis of variance (P=<0.01) the more severity of the CKD the higher the CIMT and the higher the burden of cardiovascular events



Relationship between CIMT and CKD stage

Figure1: Bar chart showing the mean CIMT in the CKD subjects as a function of their CKD stage

Correlation between CIMT and Cardiovascular risk factors

Table 2. Correlation between CIMT and Cardiovascular risk factors

PARAMETER	TEST STATISTIC	P VALUE
Age	r=+0.24	0.03
Sex	r=+16	0.17 (NS)
Duration of CKD	r=+0.24	0.04
Systolic BP	r=+0.14	0.22 (NS)
Diastolic BP	r=+0.01	0.97 (NS)
Mean Arterial Pressure	r=+0.07	0.55(NS)
BMI	r=+0.10	0.36 (NS)
Waist Circumference	r=+0.07	0.54 (NS)
Creatinine	**r=+0.78**	**<0.01**
eGFR	**r=-0.84**	**<0.01**
Haemoglobin	r=+0.05	0.69 (NS)
Fasting blood sugar	r=+0.07	0.51 (NS)
Calcium phosphate product	r=+0.10	0.40 (NS)
Proteinuria	r=+0.27	0.12 (NS)
Left ventricular hypertrophy	r=+0.714	0.29 (NS)
Total cholesterol	r=+0.01	0.95 (NS)
Triglyceride	r=+0.21	0.07 (NS)
LDL cholesterol	r=+0.05	0.62 (NS)
HDL cholesterol	r=-0.03	0.82 (NS)
Parathyroid hormone	**r=+0.73**	**<0.01**
High sensitivity CRP	**r=+0.85**	**<0.01**

Table 2. shows the univariate correlations between CIMT and some cardiovascular risk factors in CKD patients.

Predictors of CIMT

Table 3: Multiple Linear Regression for predictors of average CIMT from variables found to have a strong correlation with CIMT

Variable	Adjusted β	β	Confidence internal (B) lower	upper	P value	F	R^2
						75.301	**0.861**
Age	0.231	0.002	0.001	0.003	**<0.01**		
Serum Cr	0.156	0.008	0.001	0.014	**0.02**		
eGFR	0.176	0.003	0.003	0.005	**<0.01**		
PTH	0.218	0.001	0.001	0.001	**<0.01**		
hsCRP	0.482	0.012	0.009	0.015	**<0.01**		

Table 3 shows a multiple linear regression analysis which was used to develop a model for predicting average CIMT from age, duration of CKD, serum creatinine, eGFR, parathyroid hormone and hs-CRP levels because each of the variables had a significant correlation with CIMT. The five-predictor model was able to account for 86.1% of the variance in CIMT, F= 75.301, p<0.001, R2 = 0.861. From these predictor variables, b values (z-scores) the strongest predictor of average CIMT was high sensitivity C-reactive protein (hsCRP) with the highest adjusted b value of 0.482.

DISCUSSION

This study assessed carotid intima media thickness in 80 pre-dialysis CKD patients in stages 3 – 5 compared to healthy controls, and the prevalence and severity of CIMT as a marker of cardiovascular risks were compared between the two groups. The two groups were age and sex matched. This study shows that CKD predominantly affects young adults and middle-aged in contrast to the elderly patients seen in Europe and America [10,11]. This is similar to other studies in Nigeria and other developing countries [8,9]. The male preponderance of 1.8:1 found in this study is similar to what was reported from studies reported from other parts of the country and globally [19,20,21]. The reasons for the male CKD preponderance are still not known, however, Makusidi *et al* [22] suggested in their study that males are more financially advantaged to seek for health and the possible cultural influence of excluding women from public may have contributed to the male preponderance in their study. And since this study is hospital-based study the likelihood of male preponderance is in tandem with Makusidi *et al* whose study drew from the same cultural background.

This study found a significantly higher mean CIMT among CKD patients (0.96±0.15mm) compared to controls (0.49±0.11mm), p<0.01. The prevalence of increased CIMT in CKD patients was also significantly higher, 63.7% compared to control (0%), p <0.01. This is similar to findings reported in literature further buttressing the increased cardiovascular risk in CKD patients compared to healthy subjects since CIMT is used as a marker of atherosclerosis and increased cardiovascular risk [14,19,20].

The absolute mean CIMT of 0.96±0.15mm obtained in this study is similar to that obtained by Munna *et al* [19] however, it was higher than what was obtained by Olubukola *et al* [23]. This difference can be explained by the study protocol employed by Olubukola *et al*. They compared only hypertensive CKD patients with control thereby, did not enrol other non-hypertensive CKD patients such as DM nephropathy who have an increased risk of atherosclerotic CVD. This could contribute to the lower mean CIMT measurements as patients with DM nephropathy were found to have a higher CIMT value compared to other aetiologies of CKD in various studies [19,20]. This study enrolled a significant

number of patients with DM Nephropathy (26.5%) thereby contributing to the increased CIMT values compared to that found by Olubukola *et al*.

The mean CIMT of the control subjects in this study was 0.5±10.13 is similar to what was found by Munna *et al* who used healthy controls without hypertension or diabetes [19]. The hypertensive age and gender matched control employed by Olubukola *et al* can explain the higher mean CIMT of 0.6mm in the control group [23]. Okeahialam *et al* compared CIMT measurements between age and sex matched diabetics, hypertensives and apparently healthy individuals and found no statistically significant difference between them [24]. The mean CIMT value of the healthy control was 0.91 ± 0.13mm. This value is higher than the value obtained in this study of 0.51±0.13mm however, it is pertinent to note that CIMT measurements in the former study were carried out at 1cm proximal to the carotid bulb at both carotid arteries which usually yields a higher value compared to measurements carried out at the internal carotid artery. The average of six measurements carried out in this study may likely explain the lower mean CIMT values obtained. This difference could also be a pointer to the fact that CIMT measurements may vary from one ethnicity and location to the other even in the same country due to factors other than CVD risk factors.

The commonest underlying renal disorder in this study is CGN (32%), this finding is similar to what was reported in a study in the same institution by Makusidi *et al* [19]. A striking feature is the higher percentage of DM nephropathy (26.5%) observed in this study, taking out the possibility of selection bias, this may reflect a changing pattern of CKD epidemiology in developing countries towards non-communicable diseases. The mean CIMT in patients with DM nephropathy in this study is higher than other non-diabetic CKD though, not statistically significant. This finding is similar to what was observed by Sharshiraj *et al* [20]. The inability to establish a significant correlation between CIMT and aetiology of CKD could probably be explained by the sample size employed for the study.

This study showed a statistically significant difference in mean CIMT values across the stages of CKD. This implies that CIMT increases with decline in eGFR. Olubukola *et al* [23] did not find a significant difference in CIMT with stages of CKD however found a negative correlation between CIMT and eGFR. This difference in observations could be accounted for by relatively small sample size employed for the study and majority of the patients (57%) had stage 3 which can create an observation bias in the reference study.

This study found a positive correlation between CIMT with age, duration of CKD, serum creatinine, intact parathyroid hormone and high sensitivity CRP. A negative correlation was found between CIMT and eGFR suggesting an increase in CIMT with decline in eGFR.

Reduced renal function is an independent predictor of CIMT and a strong inverse correlation was found between CIMT and eGFR in Nigerian CKD patients [25,26]. This study found a strong association between CIMT and renal function as depicted by serum creatinine and eGFR. This is like what was reported by other authors [19,20,26]. This implies that eGFR is an independent predictor of atherosclerosis irrespective of the presence/absence of other traditional risk factors for atherosclerosis.

This study shows a significant positive correlation between hsCRP and serum creatinine on one hand and a negative correlation with eGFR on the other hand. As reported in other literatures, this study suggests that CKD is associated with inflammation as measured by hsCRP which increases with decline in renal function [25]. The use of this marker as a target for management for pre-dialysis CKD patients is suggested from this study.

The positive association between CIMT and PTH as shown in this study, suggests the role of PTH in atherosclerosis and cardiovascular disease in CKD patients [27]. The study did not find a correlation between CIMT with serum calcium, phosphate and calcium-phosphate product. This is like what was reported in recent literature [28] however, earlier studies reported a positive association in haemodialysis patients [29].

Hypertension is an important predictor of progression and mortality in CKD patients [10]. Hypertension is associated with endothelial injury and repair thereby increasing intimal media hypertrophy. This study did not demonstrate any association between systolic BP, diastolic BP, mean arterial BP and CIMT, this was also alluded to by Lawal *et al* [26]. Previous studies showed a positive correlation between blood pressure and CIMT [23]. The fact that most of the hypertensive CKD patients in this study were on antihypertensive medications may

proffer an explanation for this variation. This study also did not find any association between CIMT and other traditional risk factors for atherosclerosis such as obesity, cigarette smoking and fasting blood sugar. This finding suggests an additional non-atherosclerotic aetiology of increased CIMT in CKD patients. This may also imply that CIMT values may vary across geographical locations.

The five-model multiple linear regression in this study accounted for 86.1% of the variance in CIMT. This buttress the role of non-atherosclerotic aetiology of increased CIMT in CKD population. High sensitivity C-reactive protein was found to be the strongest predictor of CIMT in this study. C-reactive protein has been implicated in atherogenesis through activation of complements and deposition of LDL in the arterial wall [30]. The role of CRP as a predictor of CIMT was similarly demonstrated by Patel et al who assessed the markers of subclinical atherosclerosis and endothelial dysfunction in CKD patients using CIMT, hs-CRP and flow mediated vasodilation in North Indian population. They concluded that CKD confers a higher inflammatory status when compared to the general population, CRP correlated with CIMT measurements and can be used to predict cardiovascular risk in CKD patients [31].

CONCLUSION

This study found a significantly higher CIMT measurements in Nigerian CKD patients compared to age and gender matched controls.

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