

# Superficial temporal artery calcification in patients with end-stage renal disease: Association with vascular risk factors and ischemic cerebrovascular disease

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## Abstract

**Background and Purpose:** Extracranial superficial temporal artery (STA) calcification is an unusual finding seen in patients with chronic kidney disease and has unknown ramifications with respect to intracranial ischemic disease. We sought to determine the association between the risk factors for vascular calcification and this rare phenomenon, in patients with chronic renal failure, and to assess the coexistence of cerebral ischemia. **Materials and Methods:** Medical records and laboratory data on risk factors for vascular calcification were retrospectively retrieved for 453 patients with a discharge diagnosis of end-stage renal disease (ESRD). CT head examinations were reviewed to identify and associate STA calcification with 1) risk factors for the vascular calcification, 2) intracranial artery calcification, and 3) cerebral ischemia (white matter and/or cortical ischemic changes). **Results:** STA calcification was present in 9.9% (45/453) of the studied cohort. The prevalence of cerebral ischemia was 24.4% (11/45) in patients with STA calcification and 9.3% (38/408) in patients without it. Diabetes mellitus (OR: 2.56, 95% CI: 1.059–6.208;  $P=0.037$ ) was independently associated with the risk of STA calcification. The risk of cerebral ischemia, however, was not related to STA calcification ( $P=0.221$ ). **Conclusion:** The presence of diabetes mellitus is important in describing the risk of STA calcification in patients with ESRD, whereas age, gender, hypertension, serum calcium, serum phosphate, or serum hemoglobin levels are not. The risk of cerebral ischemia is not related to STA calcification but has the strongest association with diabetes mellitus.

**Key words:** Cerebrovascular disease; end-stage renal disease; superficial temporal artery calcification

## Introduction

Vascular calcification is a common complication in chronic kidney disease (CKD).<sup>[1,2]</sup> While it can occur in

the presence of normal renal function, as in the course of atherosclerosis or diabetes mellitus (DM), the prevalence and extent of vascular calcification are markedly increased in the later stages of CKD.<sup>[3]</sup> It is frequently associated with atherosclerotic lesions<sup>[2,4-8]</sup> and patients with end-stage renal disease (ESRD) or CKD-stage 5 experience markedly advanced atherosclerotic disease of the intracranial vasculature.<sup>[9,10]</sup> Vascular calcifications have a number of adverse hemodynamic consequences that can cause cardiac, vascular, and brain diseases.<sup>[4,5,11-13]</sup> However, the occurrence of superficial temporal artery (STA) calcification is much less common, even in patients with CKD.

The STA, a branch of the external carotid artery, has

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10.4103/0971-3026.85371

anecdotally been observed to demonstrate calcification on head CT examinations [Figures 1 and 2]. To the best of our knowledge, radiologically evident STA calcification has never been studied in relation to ESRD or any other clinical entity. We sought to investigate STA calcification in patients with ESRD and establish, if there was any, association between its presence and 1) the risk factors for vascular calcification; 2) intracranial carotid, vertebral, and basilar artery calcification; and 3) cerebral ischemia. Our contention was that STA calcification would be linked to risk factors for vascular calcification, have a high association with vascular calcification intracranially, and portend more severe cerebral ischemia than in those ESRD patients without STA calcification.

## Materials and Methods

### Research design and patients

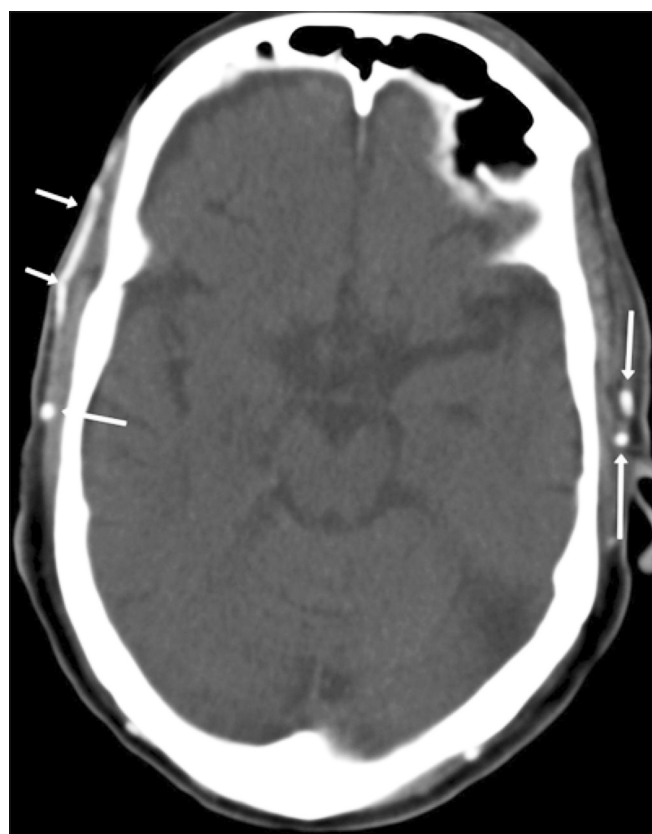
Our Institutional Review Board approved the retrospective review of patient data for this study. Informed consent was waived by the Institutional Review Board, and the study was compliant with the Health Insurance Portability and Accountability Act. Between October 2005 and December 2007, 453 patients with a discharge diagnosis code of ESRD (ICD-9 585.6) or CKD-stage 5 (ICD-9 585.5) in the electronic

patient record (EPR) were identified by the information technology group at our institution.

### Investigations

EPR software was used to retrieve laboratory data and access medical records for all the patients. Medical records were used to ascertain the following variables: age, gender, race, and documentation for established history of DM, hypertension (HTN), and laboratory data variables most temporally associated with the time of the patient's head CT scans; these included serum hemoglobin (Hb), calcium (Ca), albumin (alb), phosphorous (P), intact parathyroid hormone (iPTH), and creatinine (Cr).

CT head examinations for all patients were reviewed. All CT examinations had been performed on a multidetector computed tomography (MDCT) system. Bone window CT images were reviewed to identify calcific foci in the STA, supraclinoid segment of the internal carotid artery (ICA), the vertebral artery (VA), and the basilar artery (BA) through direct visualization of the vessels. Measurement of Hounsfield units was employed in cases of ambiguity.<sup>[14,15]</sup> Ischemic changes for white matter and/or cortical hypodensities were documented on the associated brain windows of the same CT scans. The official reports of the



**Figure 1:** Axial CT scan of the head of an 84-year-old diabetic, hypertensive male with ESRD shows multiple, bilateral, calcific foci (arrows) in the STA



**Figure 2:** Axial CT scan of the head of a 55-year-old nondiabetic, hypertensive male with ESRD shows multiple, bilateral, calcific foci (arrows) in the STA

scans were also consulted to make this determination. At the time of brain CT review for ischemic changes, the reviewers were also identifying STA calcifications but were unaware of the presence or absence of any risk factors for vascular (and by extension, STA) calcifications.

### Statistical analyses

Race was defined as “White/Other” or “African-American”; more detailed race classifications could not be used in the analysis because of the lack of representation of either the cases (those with STA calcification) or the noncases (those without STA calcification) for some of the races. Intact PTH levels were also omitted from the analysis due to a high number (53%) of unrecorded values. Serum calcium levels were corrected for serum albumin, yielding CCa (corrected calcium) levels. The mean value and standard deviation for each continuous variable (age, Hb, CCa, P, and Cr) were computed in patients with STA calcification, in patients without STA calcification, and for all patients pooled. Percentages and full counts were provided for categorical variables (gender, renal insufficiency, cerebral ischemia, ICA calcification, VA calcification, BA calcification, DM, HTN, and race) by STA calcification status and for the pooled patient sample as well.

Univariable logistic regression models for STA calcification were fitted for each variable independently.<sup>[16]</sup> A multivariable logistic regression model was also fitted to mitigate the risk of confounding.<sup>[16]</sup> Coefficients for these logistic models were presented as odds ratios. All estimates were obtained via likelihood maximization; 95% confidence intervals were constructed using normal approximations, and *P*-values were computed from the Wald Z-statistic.<sup>[16]</sup> These computations were performed using the STATA™ statistical software.<sup>[17]</sup> To obtain a more parsimonious model, a backward stepwise procedure based on minimization of the Akaike information criterion (AIC) was implemented on the full multivariable model;<sup>[16]</sup> the “step” function in the R statistical language was used for this purpose.<sup>[18]</sup>

## Results

Of 453 patients with ESRD, 9.9% (45/453) were observed to have STA calcification. Baseline features of the studied cohort, stratified by presence of STA calcification, are summarized in Table 1.

Univariable/marginal logistic models identified multiple variables to have a significant marginal association with STA calcification; these included age (*P*=0.026), Cr (*P*=0.001), ICA calcification (*P*<0.001), VA calcification (*P*<0.001), BA calcification (*P*<0.001), DM (*P*<0.001), and HTN (*P*=0.003). Cerebral ischemia (*P*=0.003) was also found to be associated with the presence of STA calcification [Table 2].

However, many of these associations reflect an indirect effect

**Table 1: Baseline features of the study population (n=453) stratified by STA calcification**

Covariate	STA calcification		Pooled (453)
	No (90.1%, 408/453)	Yes (9.9%, 45/453)	
Age	54.8 (18.1) - 0	61.1 (14.7) - 0	55.5 (17.9) - 0
Gender (Female)	39.5%, 161/408	40.0%, 18/45	39.5%, 179/453
Race (AA)	48.5%, 198/408	53.3%, 24/45	49.0%, 222/453
Hb	10.3 (2.3) - 0	10.3 (1.9) - 0	10.3 (2.3) - 0
CCa	9.4 (1.1) - 0	9.4 (0.8) - 0	9.4 (1.0) - 0
P	4.7 (2.3) - 10	5.0 (1.7) - 1	4.8 (2.2) - 11
Cr	4.0 (3.4) - 0	5.9 (3.2) - 0	4.2 (3.5) - 0
DM	30.9%, 126/408	71.1%, 32/45	34.9%, 158/453
HTN	55.6%, 227/408	80.0%, 36/45	58.1%, 263/453
ICA calcification	40.7%, 166/408	86.7%, 39/45	45.3%, 205/453
VA calcification	19.1%, 78/408	86.7%, 39/45	25.8%, 117/453
BA calcification	3.2%, 13/408	20.0%, 9/45	4.9%, 22/453
Cerebral ischemia	9.3%, 38/408	24.4%, 11/45	10.8%, 49/453

Data for continuous variables is given in the format “xx (yy) - zz,” where xx is the mean, yy the standard deviation, and zz the number of missing observations

**Table 2: Univariable/marginal logistic models of the association of risk factors with STA calcification**

Covariate	Odds ratio	95 % CI		P-value
Age	1.02	1.00	1.04	0.026
Gender (female)	1.02	0.55	1.92	0.944
Race (AA)	1.21	0.65	2.25	0.541
Hb	0.99	0.87	1.13	0.894
CCa	0.94	0.69	1.28	0.704
P	1.06	0.93	1.21	0.388
Cr	1.13	1.05	1.21	0.001
DM	5.51	2.80	10.85	<0.001
HTN	3.19	1.50	6.79	0.003
ICA calcification	9.48	3.92	22.89	<0.001
VA calcification	27.50	11.25	67.25	<0.001
BA calcification	7.60	3.04	18.98	<0.001
Cerebral ischemia	3.15	1.48	6.72	0.003

through mediating variables or are the result of confounders that were unadjusted for in the univariable models. Once proper adjustment was made for other important variables through the use of multivariable logistic models, the effect size of many of these variables decreased substantially and their association with STA calcification vanished. However, VA calcification (*P*<0.001) and DM (*P*=0.037) maintained their association with STA calcification. After adjusting for all other variables, the odds of STA calcification were 14 times (OR: 13.93, 95% CI: 4.56–42.56; *P*<0.001) higher in patients with VA calcification compared to patients without VA calcification; similarly, the odds of STA calcification were 2.6 times higher (OR: 2.56, 95% CI: 1.06–6.21; *P*=0.037) in patients with DM compared to patients without DM. After

adjustment for confounding variables, cerebral ischemia ( $P=0.221$ ) was observed to be no longer associated with the presence of STA calcification [Table 3].

A multivariable logistic model with cerebral ischemia as outcome identified DM (OR: 2.37, 95% CI: 1.19–4.74;  $P=0.014$ ) as the only variable independently associated with its risk. However, a parsimonious model based on AIC minimization not only showed a strengthened association of DM but also revealed VA calcification as important in describing the risk of cerebral ischemia.

## Discussion

Vascular calcification is a frequent complication in CKD.<sup>[1,2]</sup> It occurs in two distinct forms: arterial intima calcification and arterial media calcification (AMC).<sup>[2,7]</sup> Arterial intima calcification is seen in the advanced stages of atherosclerosis<sup>[2,4-8]</sup> and patients with ESRD experience markedly advanced atherosclerotic disease of the cerebral vasculature.<sup>[9,10]</sup> AMC or Mönckeberg arteriosclerosis is frequently seen in ESRD and is associated with aging, presence and duration of diabetes, and uremia. It is observed to have a predilection for muscle-type conduit arteries such as the femoral, tibial, and uterine arteries.<sup>[8,19]</sup> Vascular calcification is an indicator of a number of adverse hemodynamic consequences<sup>[11,12]</sup> and is frequently associated with stroke, myocardial ischemia, and peripheral vascular occlusive disease (PVOD).<sup>[4-6,13]</sup> In this study, we identified the risk factors for STA calcification and examined its association with ischemic cerebrovascular disease. As far as we are aware, this is the first study to examine the risk factors and outcomes for STA calcification in patients with ESRD.

Of the studied risk factors for vascular calcification, only DM was found to be significantly associated with

STA calcification. Age, Cr, and HTN demonstrated only marginal associations. The risk factors that did not show any association whatsoever included gender, race (AA), Hb, CCa, and P.

## Epidemiologic factors

Various studies have noted an age-related increase in vascular calcification.<sup>[4,14,15,20-24]</sup> Braun *et al.*,<sup>[20]</sup> documented an age-related increase in coronary artery calcification in 49 chronic hemodialysis and 102 nondialysis patients, with the hemodialysis group demonstrating an exaggerated increase. A similar trend was noticed for coronary artery calcification in patients with childhood-onset CKD,<sup>[4,21]</sup> intracranial artery calcification (IAC),<sup>[14,22]</sup> and cervical carotid<sup>[15,23]</sup> and cavernous carotid artery calcification.<sup>[24]</sup> STA is fundamentally different from coronary, carotid, and intracranial arteries; the latter have well-established association with atherosclerosis<sup>[14,25]</sup> which increases with age<sup>[25]</sup> and is frequently associated with arterial intima calcification.<sup>[2,4-8,14]</sup> Gender preponderance has been investigated in relation to vascular calcification. Our observation of gender-neutrality is in agreement with various studies.<sup>[4,13,14,24,26,27]</sup> However, male gender preponderance has been reported for coronary artery calcification in patients with ESRD<sup>[28]</sup> and for intracranial ICA calcification.<sup>[22]</sup>

## Serum markers

Hypercalcemia, hyperphosphatemia, and increased iPTH have been associated with vascular calcification in a number of studies.<sup>[4,21,27-31]</sup> Others, in contrast, have found no such association.<sup>[14,20,26]</sup> Moreover, various studies have linked Cr to the risk of vascular calcification,<sup>[14,21,32]</sup> which is in contrast with our observation. These differences may be related to the difficulty of relating a long-term process such as calcification to parameters such as Ca, P, and Cr, which are rarely constant in patients with ESRD who frequently undergo dialysis. This issue can be circumvented by using averaged values over a longer period of time. We could not use averaged out values because, for a considerable number of patients, only a few values of the aforementioned serum markers were available. We did not find any correlation between Hb levels and STA calcification, which is a reiteration of what has been documented before for coronary artery,<sup>[28]</sup> aorta, common carotid and femoral artery,<sup>[26]</sup> and IAC.<sup>[14]</sup>

## Diabetes mellitus and hypertension

Patients with DM had 2.6 times greater odds of STA calcification than those without DM. A similar association has been documented by various other studies in the coronary,<sup>[28]</sup> peripheral,<sup>[33]</sup> and intracranial vasculature.<sup>[14]</sup> DM is a well-established risk factor for vascular calcification. AMC or Mönckeberg sclerosis, which is observed with high frequency in patients with hypervitaminosis D, ESRD, DM, and nondiabetic neuropathies,<sup>[25]</sup> is particularly related to

**Table 3: Multivariable logistic models of the association of risk factors with STA calcification**

Covariate	Odds ratio	95 % CI	P value
Age	0.99	0.96 1.02	0.440
Gender (Female)	0.73	0.28 1.89	0.512
Race (AA)	0.86	0.35 2.09	0.738
Hb	0.93	0.77 1.13	0.487
CCa	1.08	0.69 1.68	0.738
P	0.96	0.77 1.19	0.694
Cr	1.05	0.87 1.26	0.639
DM	2.57	1.06 6.21	0.037
HTN	1.03	0.37 2.86	0.953
ICA calcification	1.45	0.42 4.93	0.554
VA calcification	13.94	4.56 42.56	<0.001
BA calcification	3.37	0.91 12.46	0.068
Cerebral ischemia	1.89	0.68 5.21	0.221



the presence and duration of DM.<sup>[8,19,25,34,35]</sup> AMC is also known to have a predilection for muscle-type conduit arteries such as femoral, tibial, and uterine arteries,<sup>[8,19]</sup> which further explains the observed relation between DM and STA (a medium-sized muscular artery) calcification. Data on the role of HTN as a risk factor for vascular calcification are contradictory at best. Some studies have reported a significant association between HTN and vascular calcification,<sup>[14,20,36]</sup> while others have observed lack thereof.<sup>[4,22,26]</sup> One study has noted a negative association between diastolic blood pressure and calcification score.<sup>[13]</sup> We observed only a marginal association between HTN and STA calcification.

### Intracranial artery calcification

The prevalence of STA calcification in the studied cohort was 9.9% (45/453). To the best of our knowledge, radiographically evident STA calcification has never been studied in relation to ESRD or any other clinical entity. ICA calcification was observed in 45.3% (205/453), VA calcification in 25.8% (117/453), and BA calcification in 4.9% (22/453) of cases. Similar proportions, albeit with higher prevalence in individual categories, have been observed in many reports.<sup>[14,36,37]</sup> Higher prevalence in individual categories was observed in reports on ischemic stroke patients.<sup>[14,37]</sup> VA calcification was noted to have an unusually strong association with STA calcification. The existing literature does not suggest any rationale for this observation. We believe the comparable size of the two arteries could offer an explanation and this merits further investigation from the perspective of hemodynamic stress.

### Cerebral ischemia

There was no association between cerebral ischemia and STA calcification in our study. Cerebral ischemia was, however, associated with VA calcification but not with ICA calcification. Various studies have investigated the association between IAC and cerebral ischemia but there have been conflicting results.<sup>[14,22,24,37,38]</sup> Bugnicourt *et al.*,<sup>[14]</sup> and Chen *et al.*,<sup>[37]</sup> studied IAC in various segments [ICA, VA, middle cerebral artery (MCA), and BA] and documented a higher frequency of IAC in stroke than in nonstroke patients. They did not report separate associations for ICA calcification, VA calcification, and BA calcification. Other reports investigated intracranial ICA calcification<sup>[22,24,38]</sup> and concluded that calcification was not associated with ischemic cerebrovascular disease,<sup>[22]</sup> MR imaging white matter scores,<sup>[24]</sup> or MCA and non-MCA infarctions. Cerebral ischemia also demonstrated a significant association with DM. DM is a well-established “modifiable” risk factor for stroke,<sup>[39]</sup> an association reiterated in this study.

This study has a number of limitations. Our single-center cohort lacked a matched control group (without ESRD). Sample selection was based on discharge diagnosis of ESRD, which was not accurately representative of the disease stage

at the time of CT scan in a number of cases (162/453; 35.8%). Further, risk factors like dyslipidemia and inflammatory markers (C-reactive protein, fibrinogen) could not be studied and others like iPTH and race variables other than AA could not be analyzed. We have not looked at diabetic patients without renal disease to see if the STA calcification precedes the onset of renal insufficiency or portends this. Lastly, we were unable to use averaged values of serum markers and we did not compute creatinine clearance.

### Implications for care

This study is the first one to investigate STA calcification in relation to risk factors for intracranial vascular calcification and cerebral ischemia. It opens an avenue for further investigations of the same kind, which should be modified and refined to elude better associations.

### Conclusion

The presence of DM is important in describing the risk of STA calcification in patients with ESRD, whereas age, gender, HTN, Ca, P, and Hb levels are not. The risk of cerebral ischemia is not related to STA calcification but is strongly associated with DM and further characterized by VA calcification.

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**Cite this article as:** Anwar Z, Zan E, Carone M, Ozturk A, Sozio SM, Yousem DM. Superficial temporal artery calcification in patients with end-stage renal disease: Association with vascular risk factors and ischemic cerebrovascular disease. *Indian J Radiol Imaging* 2011;21:215-20.

**Source of Support:** Nil, **Conflict of Interest:** None declared.

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