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REVIEW

- 86 Contrast-induced acute kidney injury: A review of practical points
Ozkok S, Ozkok A
- 100 Role of different imaging modalities of vascular calcification in predicting outcomes in chronic kidney disease
Disthabanchong S, Boongird S
- 111 Targeting cannabinoid signaling for peritoneal dialysis-induced oxidative stress and fibrosis
Yang CY, Chau YP, Chen A, Lee OKS, Tarng DC, Yang AH

MINIREVIEWS

- 119 Cold dialysis and its impact on renal patients' health: An evidence-based mini review
Sakkas GK, Krase AA, Giannaki CD, Karatzaferi C
- 123 Role of imaging in the evaluation of renal dysfunction in heart failure patients
Grande D, Terlizzese P, Iacoviello M

ORIGINAL ARTICLE

Case Control Study

- 132 Any link of gout disease control among hypertensive patients and onset of end-stage renal disease? Results from a population-based study
Perreault S, Nuevo J, Baumgartner S, Morlock R

Retrospective Study

- 143 Advanced wasting in peritoneal dialysis patients
Xu Z, Murata GH, Glew RH, Sun Y, Vigil D, Servilla KS, Tzamaloukas AH
- 150 Clinicopathological spectrum of snake bite-induced acute kidney injury from India
Vikrant S, Jaryal A, Parashar A
- 162 Acute kidney injury from different poisonous substances
Naqvi R

ABOUT COVER

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Role of different imaging modalities of vascular calcification in predicting outcomes in chronic kidney disease

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Abstract

Vascular calcification (VC) is common among patients

with chronic kidney disease (CKD). The severity of VC is associated with increased risk of cardiovascular events and mortality. Risk factors for VC include traditional cardiovascular risk factors as well as CKD-related risk factors such as increased calcium and phosphate load. VC is observed in arteries of all sizes from small arterioles to aorta, both in the intima and the media of arterial wall. Several imaging techniques have been utilized in the evaluation of the extent and the severity of VC. Plain radiographs are simple and readily available but with the limitation of decreased sensitivity and subjective and semi-quantitative quantification methods. Mammography, especially useful among women, offers a unique way to study breast arterial calcification, which is largely a medial-type calcification. Ultrasonography is suitable for calcification in superficial arteries. Analyses of wall thickness and lumen size are also possible. Computed tomography (CT) scan, the gold standard, is the most sensitive technique for evaluation of VC. CT scan of coronary artery calcification is not only useful for cardiovascular risk stratification but also offers an accurate and an objective analysis of the severity and progression.

Key words: Coronary calcification; Aortic calcification; Hemodialysis; Dialysis; Ultrasound; Mammogram; Plain X-ray

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Core tip: Vascular calcification (VC) is common among patients with chronic kidney disease. VC is observed in arteries of all sizes. Several imaging techniques have been utilized in the evaluation of VC. Plain radiographs are simple, readily available and can somewhat differentiate between intimal and medial calcification. Mammography detects medial calcification and is especially useful among women. Ultrasonography is suitable for superficial arteries. Analyses of wall thickness and lumen size are possible. Computed tomography, the gold

standard, is the most sensitive technique and offers the most accurate analysis of the severity and progression of VC.

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INTRODUCTION

Vascular calcification (VC) is common among patients with chronic kidney disease (CKD). The severity of VC is associated with increased risk of cardiovascular events and mortality. Several risk factors specific to CKD population including increased calcium and phosphate load and loss of calcification inhibitors influence the development and the progression of VC. In CKD, VC is observed in arteries of all sizes from small arterioles to aorta and are located in the intima and/or the media of arterial wall. Intimal calcification occurs predominantly in large arteries in association with atherosclerotic plaques resulting in lumen narrowing. Medial calcification can occur in larger arteries as well as smaller muscle-type arteries and arterioles. The lumen of the artery with medial calcification is largely patent but the wall is hardened causing poor arterial compliance and decreased blood flow. Similar to general population, the degree of VC in CKD is strongly associated with cardiovascular (CV) disease and mortality. The review of pathogenesis and clinical implications of VC can be found elsewhere^[1]. Different imaging modalities ranging from simple plain radiographs to computed tomography (CT) have been utilized in the examination and the quantification VC. The present review focuses on different imaging techniques and their abilities to predict long-term outcomes in CKD population.

PLAIN RADIOGRAPHS

Several types of plain radiograph have been used to detect and quantify the amount of VC in different areas of the body. Plain radiographs are cheap, readily available and have the advantage of being able to somewhat differentiate between intimal and medial calcification.

Lateral lumbar spine radiograph

Lateral lumbar spine X-ray has been utilized in the evaluation of atherosclerosis and calcification of abdominal aorta since 1950s (Figure 1)^[2,3]. In 1980s, the relationship between aortic calcification in the pre-lumbar region and the risk of future CV death was documented^[4]. In 1997, using lateral lumbar spine X-rays from 617 Framingham heart study participants, Kauppilla *et al.*^[5] established a simple scoring method that provided a simple and low

cost assessment of the degree of atherosclerotic vascular disease. In two large cohorts of men and women without CKD, this semi-quantitative measurement showed the ability to predict future coronary artery disease (CAD), congestive heart failure, CV events and CV mortality^[6,7]. When applying Kauppila score to hemodialysis patients, the degree of calcification was highly correlated with coronary artery calcification score (CAC score) obtained from the electron beam CT and arterial stiffness analyzed by the pulse wave velocity (PWV)^[8,9]. In two large cohorts of maintenance hemodialysis patients, Kauppila score could predict all-cause and CV mortality and non-fatal CV events^[10,11]. Due to such evidence, the 2009 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommended lateral lumbar spine X-ray for the assessment of VC burden in dialysis patients^[12]. Few studies have also reported the use of lateral abdominal X-ray in non-dialysis CKD population^[13,14]. The calcification score obtained from lateral lumbar spine radiograph was highly correlated to the score obtained by CT^[15]. As kidney function declined, the degree of calcification increased and Kauppila score ≥ 4 predicted future CV events^[16,17]. Tables 1 and 2 summarize different imaging techniques, the predictable outcomes and the available scoring systems associated with them.

Chest radiograph

Aortic arch calcification can readily be seen in a postero-anterior (PA) or antero-posterior chest X-ray and the entire aortic arch can be visualized in a lateral chest radiograph (Figure 2). The prognostic significance of aortic arch calcification has been described since 1950s^[18,19]. In the Framingham cohort, the degree of thoracic aortic calcification doubled with each decade of age and its presence was associated with a twofold increase in the risk of CV death, CAD, stroke and peripheral arterial disease (PAD)^[20]. In another cohort of over 100000 men and women in United States, the presence of aortic arch calcification on PA chest X-ray was associated with older age, smoking, hypertension and elevated cholesterol and increased the risk of CAD and stroke^[21]. In dialysis population, a simple scoring system of aortic arch calcification in PA chest X-ray was devised by Ogawa *et al.*^[22] that showed high correlation with calcification score obtained by CT. The severity of aortic arch calcification correlated with age, dialysis vintage, PWV, cardiothoracic ratio and parathyroid hormone level and displayed the ability to predict future CV events and mortality^[23-26]. In peritoneal dialysis patients, the severity and progression of aortic arch calcification were independent predictors of all-cause and CV mortality^[27]. In addition to the PA view, lateral chest X-ray offers another viewing angle of the entire aortic arch. The analysis of progression of aortic arch calcification on lateral chest X-ray in chronic dialysis patients revealed the association with hypercalcemia, hyperparathyroidism and future all-cause and CV mortality^[28]. In the recent meta-analysis that included 3256 dialysis patients, the presence of aortic arch

Table 1 Summary of different imaging modalities for vascular calcification in chronic kidney disease

Types of X-rays	Calcification area	Advantages	Limitations	Scoring methods	Outcomes prediction
Plain radiography					
Lateral lumbar spine	Abdominal aorta	Simple	Subjective quantification	Kauppila <i>et al</i> ^[5] Ogawa <i>et al</i> ^[22]	CV events, mortality
Postero-anterior chest	Aortic arch	Simple, readily available in almost all patients			
Lateral chest	Aortic arch	Simple	Noordzij <i>et al</i> ^[28] Adragão <i>et al</i> ^[33]		Mortality
Antero-posterior pelvis	Iliac and femoral arteries	Simple, allow differentiation between intimal- and medial-type calcification			
Hand	Radial, ulnar and digital arteries	Simple, allow analysis of medial-type calcification		Adragão <i>et al</i> ^[33]	Outcome data is lacking
Foot	Tibial, dorsalis pedis, plantar and digital arteries				
Mammography	Intramammary arteries	Readily available in most women, allow analysis of medial-type calcification	Subjective quantification	Not available	PAD events
Ultrasonography	Carotid, femoral and peripheral arteries	No radiation exposure, allow evaluation of arterial wall thickness and lumen size	Only superficial arteries can be evaluated, subjective quantification	Not available	CV events, mortality
Computed tomography					
Chest	Coronary arteries	Intravenous contrast is not required, the most objective and reproducible quantification which allows analysis of progression	Cost, radiation exposure, does not allow differentiation between intimal- and medial-type calcification	Agatston <i>et al</i> ^[63] Callister <i>et al</i> ^[100]	CV events, mortality
Abdomen	Thoracic aorta Abdominal aorta				
				Hong <i>et al</i> ^[101]	CV events, mortality

CV: Cardiovascular; PAD: Peripheral arterial disease.



Figure 1 Abdominal aortic calcification seen on lateral lumbar spine radiograph.

calcification was associated with a greater risk of CV and overall mortality^[29].

Pelvic radiograph

Pelvic X-ray can be used to evaluate calcification in iliac and femoral arteries. As mentioned above, in peripheral branches of aorta, the prevalence of medial calcification increases. Intimal and medial calcification can be somewhat differentiated by different characteristics seen on plain X-rays. The discrete plaque with irregular and patchy distribution represents calcification in the intima, whereas the uniform linear railroad track-type is the characteristic of calcification in the media (Figure 3)^[30,31]. The presence of medial calcification in diabetic patients is a strong predictor of future CV events, stroke, PAD

and mortality^[30]. In hemodialysis patients, the presence of medial calcification in iliac and/or femoral arteries in pelvic X-ray was not associated with aging, CV disease or diabetes but rather related to prolonged dialysis vintage, increased serum calcium, phosphate, parathyroid hormone and the dose of calcium binder suggesting the close relationship between medial calcification and uremic milieu^[31]. Both intimal and medial calcification seen on pelvic X-ray showed the ability to predict overall and CV mortality in hemodialysis patients^[31]. A simple VC score of the medial-type calcification seen on pelvic X-ray and bilateral PA view of both hands was introduced by Adragao *et al*^[32]. Increased Adragao score in hemodialysis patients was positively correlated with arterial stiffness, future CV events and mortality^[33]. The degree of pelvic arterial calcification showed 67% sensitivity and 85% specificity for the prediction of CAC score ≥ 100 and above 80% sensitivity and specificity for the prediction of CAC ≥ 400 ^[34].

Hand and foot radiographs

The presence of calcification in small arteries of hands and feet are largely due to medial calcification, therefore, the linear tram-track calcification along the length of the artery is a typical finding (Figure 4). The earlier study of calcification of small arteries in hands and feet of diabetic patients revealed the association between medial calcification and microvascular complications (diabetic neuropathy, retinopathy and nephropathy)^[35]. In patients taking warfarin, the increase in VC in ankle and foot that was limited to a medial pattern was observed^[36]. In CKD

Table 2 Summary of scoring systems for vascular calcification in chronic kidney disease

Scoring methods	Calcification area	Details
Kaupila <i>et al</i> ^[5]	Abdominal aorta between L1-L4 in a lateral lumbar spine radiograph	The length of calcification in the anterior and posterior wall of the aorta in front of each vertebra is scored between 0-3. Total score is the sum of calcification in both walls of the aorta between L1-L4
Ogawa <i>et al</i> ^[22]	Aortic knob in a PA chest radiograph	A scale with 16 circumferences is attached to the aortic knob. The number of sections with calcification are counted
Noordzij <i>et al</i> ^[28]	Aortic arch in a lateral chest radiograph	Visual inspection of calcification. The degree of calcification is categorized into no (score 0), moderate (score 1) or severe (score 2) calcification
Adragao <i>et al</i> ^[32]	Iliac and femoral arteries in a pelvic radiograph and arteries of both hands in a bilateral hand radiograph	The pelvic radiograph is divided into four sections by a horizontal line over the top of both femoral heads and a vertical line over the vertebral column. The bilateral hand radiograph is divided by a vertical line which separates each hand and a horizontal line over the top of metacarpal bones. The presence of linear calcifications in each section is counted as 1
Agatston <i>et al</i> ^[63] (CAC score by area)	Coronary arteries in a thoracic CT scan	CT images of 3 mm thickness are acquired from the carina to the diaphragm. The calcified lesion in coronary arteries is the area of at least 0.5 mm ² that has a threshold density ≥ 130 HU. The density score 1 = 130-199 HU, 2 = 200-299 HU, 3 = 300-399 HU and 4 ≥ 400 HU. The calcification area is then multiplied by the density score
Callister <i>et al</i> ^[100] Hokanson <i>et al</i> ^[102] (CAC score by volume)	Coronary arteries in a thoracic CT scan	Coronary calcium volume score is obtained from the multiplication of calcification area by the section thickness. A square root is applied to the volume score in order to decrease the variability among those with high scores
Hong <i>et al</i> ^[101] (Calcium mass score)	Coronary arteries in a thoracic CT scan	Measurement of the absolute mass of CaHA. The procedure uses a phantom containing different concentrations of CaHA placed beneath the thorax in order to calibrate the segmented coronary calcium. The absolute score is expressed as milligrams of CaHA
Moe <i>et al</i> ^[83] Chertow <i>et al</i> ^[103] Yildiz ^[104] DeLoach ^[105]	Different portions of thoracic aorta visualized in a thoracic CT scan	The scores are based on the area calcification as described by Agatston <i>et al</i> or the volume calcification as described by Callister <i>et al</i> or Hokanson <i>et al</i>
Kabaya <i>et al</i> ^[106] Taniwaki <i>et al</i> ^[107] Yamada <i>et al</i> ^[108] (Aortic calcification index)	Abdominal aorta 10-15 cm in length above the bifurcation in abdominal CT scan	Abdominal aorta is evaluated in 10-15 CT slices at 0.8-1 cm interval. The proportion of aortic circumference covered by calcification is quantified in relation to the total circumference in each slice. The score is total calcification in all slices

CT: Computed tomography; CaHA: Calcium hydroxyapatite.

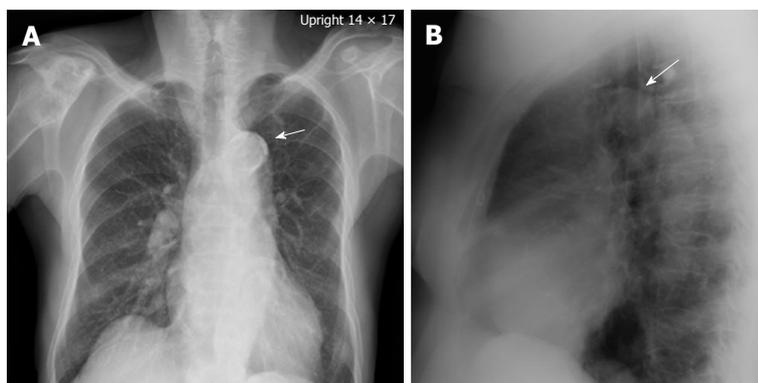


Figure 2 Aortic arch calcification (arrow) seen on postero-anterior chest radiograph (A) and lateral chest radiograph (B).

patients, the earliest and commonest sites of calcification were ankles, followed by feet, hands and wrists^[37]. Longer dialysis vintage and increased serum phosphate were positively associated with VC of hand arteries whereas PAD was associated with VC of foot arteries^[38,39].

MAMMOGRAPHY

In 1980, the presence of intramammary arterial calcifications characterized as linear tram-track medial-type calcification was reported in association with diabetes

(Figure 5)^[40]. The subsequent study that performed a biopsy of such calcification confirmed the histologic finding of medial calcification^[41]. In women over 40-50 years of age, the presence of breast arterial calcification (BAC) was associated with CV disease and portended a markedly increased risk of CV events and mortality^[42-45]. In women taking warfarin, the prevalence of BAC was 50% greater than those not taking the drug and increased with the duration of therapy reaching as high as 75% in patients with at least 5 years of exposure^[46]. In CKD patients, BAC occurred more frequently than non-CKD subjects with the



Figure 3 Plaque-like intimal calcification (black arrow) and uniform linear railroad track-like medial calcification (white arrow).

prevalence of 25% in CKD stage 3, 40% in CKD stages 4-5 and over 60% in CKD stage 5D compared to 20% in age and diabetes-matched non-CKD subjects^[47]. Increased severity of BAC was associated with aging, diabetes and dialysis duration and predicted new PAD events^[48].

ULTRASONOGRAPHY

Ultrasonography has the benefit of no radiation exposure and offers a unique mean to evaluate arterial wall thickness and lumen size. The resolution of ultrasound depends on the depth of field, therefore, ultrasound is suitable for imaging of superficial arteries such as carotid, femoral and peripheral arteries. The quantification is largely subjective and operator dependent. Ultrasound assessment of carotid arterial atherosclerotic disease has become the first choice for screening of carotid artery stenosis. Carotid intima-media thickness (IMT) is also an early atherosclerotic risk marker, therefore, most studies focus on carotid IMT rather than calcification, which is a late event. The review of carotid IMT and outcomes is beyond the scope of this review. In elderly subjects, calcified carotid plaques predicted mortality and CV outcomes independent of traditional CV risk factors^[49]. In ESRD patients, calcified plaques in carotid and femoral arteries were present in 71% compared to 21% in age-matched control^[50]. Patients with calcification were significantly older, predominantly male, and had a higher prevalence of previous CV disease. The presence of calcification was associated with increased carotid IMT and higher number of plaques^[51]. Another study in hemodialysis patients found the association between carotid calcification with age, duration of dialysis, calcium x phosphate product and prescribed dose of calcium-based phosphate binder^[52,53]. Carotid arterial calcification was also an independent risk factor for composite CV events in incident hemodialysis patients^[54]. Similarly, in peritoneal dialysis patients, the prevalence of carotid calcification was high and was associated with diabetes mellitus, increased left ventricular mass index, and lower survival rate^[55]. The calcification score of combined sites evaluated by both ultrasonography and plain X-rays of

carotid artery, abdominal aorta, iliofemoral axis, and legs predicted all-cause and CV mortality^[56].

CT

Non-contrast CT is the gold standard for detection and quantification of VC. CT is equipped with a software program which allows a more sensitive and objective quantification of calcification. Multi-slice CT has largely replaced electron beam CT due to its improved image quality, accuracy and reproducibility^[57]. Due to high sensitivity and accuracy, analyses of progression or changes after treatment are possible. CT of large arteries such as aorta and its branches and coronary arteries have been utilized to classify CV risk in both general and CKD populations. The disadvantage of CT lies in the cost and the amount of radiation exposure which is approximately 30 times higher than a plain X-ray^[58]. CT does not differentiate between intimal and medial calcification and may not be suitable for evaluation of medial-type calcification in small arteries.

Coronary arteries

The significance of CAC detected by CT (Figure 6) has been recognized since 1980s^[59]. The presence of CAC was associated with aging, hypertension, diabetes, obesity, hyperlipidemia, angiographic coronary stenosis and histopathologic atherosclerosis^[60-62]. The quantification method of CAC reported by Agatston *et al.*^[63] showed excellent inter-observer agreement and has the ability to predict CV events with high sensitivity and specificity^[63-65]. The Expert Consensus Document of the American College of Cardiology/American Heart Association stated that the sensitivity and specificity of CT in detection of coronary artery stenosis or occlusion was 90.5% and 49.2% respectively^[66]. When the prognostic accuracy of CAC score was evaluated in a large cohort of asymptomatic subjects between 50-70 years of age, CAC score was able to predict CAD events independent of standard CV risk factors and was superior to the Framingham risk index in predicting the events^[67]. When compared to thoracic and abdominal aortic calcification, CAC was most strongly associated with major CAD events, followed by major CV events, and all-cause mortality independent of Framingham risk factors^[68]. In CKD, increased prevalence and severity of CAC are well documented. The prevalence upto 80%-90% has been reported in ESRD population^[69-72]. In dialysis patients, the degree of CAC was more pronounced in older patients, male gender, patients with diabetes, longer dialysis vintage, high serum calcium and phosphate and high calcium intake^[69,70]. Similar to general population, the severity of CAC in dialysis patients predicted early mortality after adjustments for other risk factors^[73,74]. In non-dialysis CKD stages 3-5, the prevalence of CAC was as high as 40%-70% compared to 13% in age-matched non-CKD subjects and the severity was 10 times that of general population^[75,76]. A strong and graded relationship

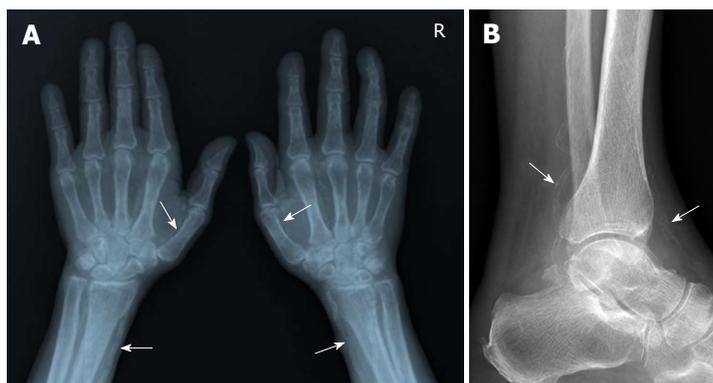


Figure 4 Medial calcification in small arteries in hands (A) and foot (B).

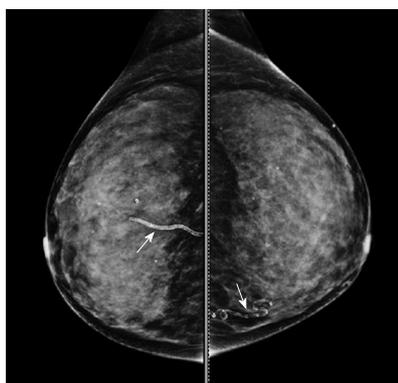


Figure 5 Breast arterial calcification with the typical linear tram-track medial-type calcification (arrows).

between lower estimated glomerular filtration rate (eGFR) and increasing CAC was documented^[76]. Aging, diabetes, male gender, body mass index, eGFR and serum phosphate were associated with the degree of CAC and the rapid progression rate was observed paralleling the severity^[77-79]. The presence of CAC in non-dialysis CKD also adversely affected patient survival and the addition of CAC score to traditional risk factors improved the prediction of CV risks in non-dialysis CKD population^[15,80].

Aorta

The evaluation of abdominal aortic calcification by CT has been reported since 1984^[81]. Similar to CAC, aortic calcification likely influences subsequent CV events. Different areas of the aorta from the arch to the bifurcation have been chosen by different investigators^[82]. In general, atherosclerosis and calcification are observed more frequently at the bifurcation where turbulent flow occurs, therefore, several investigators chose the part of abdominal aorta just above common iliac arteries. Several scoring methods have been devised that can largely be categorized into two types of techniques; the first technique is based on Agatston's method or "calcification score by area" and the other technique is "calcification score by volume"^[83]. Different terms have been used for the quantification method such as aortic calcification area index, aortic calcification index,

aortic calcification volume, etc^[82]. Aortic calcification normally appears approximately a decade after CAC. Aging, male gender, diabetes and hypertension are among important risk factors. At the age of 50, the prevalence of abdominal aortic calcification is 15%-20% and increases to 90% by the age of 70^[84]. The degree of thoracic aortic calcification (excluding aortic arch and proximal descending aorta) evaluated in the CT scan originally aimed at CAC assessment (Figure 6) was found to predict CV events, CV mortality and all-cause mortality albeit with much less robustness than CAC^[85-87]. The recent study also suggested that thoracic aortic calcification might not improve the 10-year estimation of prognosis beyond traditional risk factors^[88]. Normally, the aortic arch and the proximal descending aorta have much more concentrated calcification than the descending thoracic aorta^[89]. In a cohort of elderly subjects, aortic arch calcification predicted CV and all-cause mortality and addition of aortic arch calcification to CAC score moderately improved the predictive value for outcome^[90]. The prognostic significance of abdominal aortic calcification beyond the Framingham risk factors has also been documented^[68]. In a large cohort of over 2000 men and women, abdominal aortic calcification above the bifurcation of iliac arteries was predictive of CAD and CV events as well as CV and overall mortality^[91]. In hemodialysis patients, the prevalence of aortic calcification was high and the severity was associated with aging, male gender, diabetes, increased systolic blood pressure, increased serum calcium and phosphate and longer dialysis vintage^[92,93]. Aortic calcification was observed with increasing frequency from the thoracic aorta to upper abdominal aorta and lower abdominal aorta^[94]. In two cohorts of maintenance hemodialysis patients, abdominal aortic calcification predicted CV and overall mortality and nonfatal CV events^[93,95]. Calcification of the lower part of abdominal aorta appeared to be the most predictive of CV events and mortality^[94]. In non-dialysis CKD patients, the prevalence of calcification in abdominal aorta was 50% in CKD stage 3 and 80%-90% in CKD stages 4-5. The degree of VC was associated with aging, declining renal function, increasing serum phosphate and high PWV^[16,96,97]. With advancing CKD

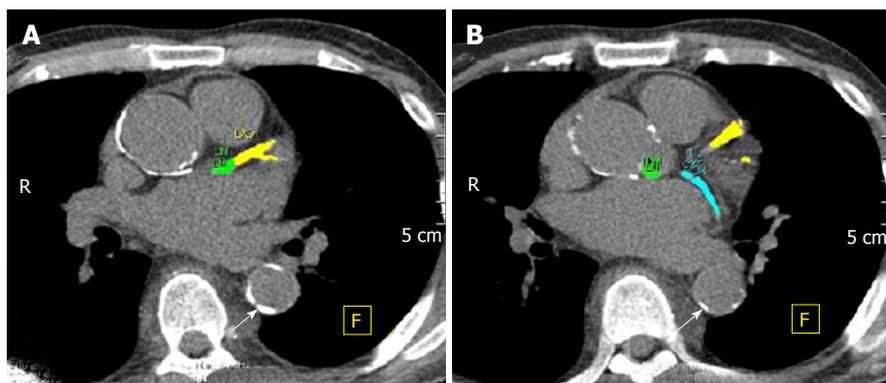


Figure 6 Coronary artery calcification (marked with colors) and descending thoracic aortic calcification (arrows) seen on non-contrast multislice computed tomography.

stages, the progression occurred more rapidly^[98]. The severity of calcification was an independent predictor for de novo CV events in CKD stages 4-5 patients^[99].

CONCLUSION

In summary, VC can be detected by several imaging techniques. Plain radiographs are simple and readily available and the presence of VC can be examined in a single X-ray film. Plain radiographs also allow differentiation between intimal and medial calcification, which comes in useful in CKD population. Mammography is especially advantageous among women because the severity of medial calcification can be assessed in images acquired during the routine screening mammogram. Ultrasonography offers a mean to evaluate arterial wall thickness and lumen size as well as calcification with the benefit of no radiation exposure. CT scan, the gold standard, is the most sensitive technique that offers an accurate and an objective analysis of the severity of VC. Plain radiographs are appropriate in situations where risk evaluation is the main focus, whereas CT scan is indispensable for accurate analysis of progression or changes after intervention.

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