3f Detection and evaluation

Should nephrologists consider vascular calcification screening?

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Abstract

Vascular calcification (VC) has been widely reported over the last few decades and is associated with significant morbidity and mortality among patients with chronic kidney disease (CKD). Importantly, these patients have premature and rapidly progressive calcification when compared to the general population. VC is an active and complex process that is closely regulated by a growing list of inducers and inhibitors. VC can be detected using several non-invasive modalities including plain radiography, echocardiogram and computed tomography scans. However, the usefulness of these imaging measurements to capture treatment effects is limited. Routine screening and monitoring for progression of VC remains highly debatable.

Introduction

The burden of vascular calcification in chronic kidney disease

Vascular calcification (VC) is a major contributor to cardiovascular (CV) disease burden among patients with chronic kidney disease (CKD). The age and gender –standardised risk of VC is 2- to 5-fold higher in patients with CKD compared to the general population[1, 2]. VC is characterised by intimal and medial wall thickening and loss of elasticity, primarily through accelerated atherosclerosis and arteriosclerosis[3]. VC is an active and complex process closely regulated by a growing list of inducers and inhibitors, including phosphate, calcium, inflammatory cytokines, fetuin-A, matrix Gla protein, osteoprotegerin and pyrophosphate[4]. Accelerated atherosclerosis and calcification of both medial and intimal layers of coronary and systemic arteries results in reduced coronary perfusion and increased arterial stiffness, and subsequently contributes to adverse CV events and mortality among patients with CKD[5-7]. In fact, the odds ratio for any CV event in the presence of VC was reported to be 6-fold higher among patients with CKD[8]. Due to this direct link to adverse outcomes, VC assessment has gained tremendous interest as a screening tool to refine CV risk stratification and as a surrogate end-point for various CV interventions.

Assessment of vascular calcification

The Kidney Disease: Improving Global Outcomes (KDIGO) 2009 guidelines for Chronic Kidney Disease and Mineral and Bone disorders (CKD-MBD) summarised the prevalence and methods of VC assessment based on 25 studies from 2001-2009[9]. Six of these studies were conducted in CKD stage 3-5 and the remaining studies involved patients on dialysis. A range of methods of VC assessment were utilised in these observational studies including pulse pressure, valvular calcification [using echocardiogram and computed tomography (CT) scan], abdominal aortic calcification (using plain X-ray and CT), intimal-media thickness (IMT) of the carotid arteries and coronary artery calcium score (CACS) using CT, resulting in a wide variation of the reported prevalence of both vascular and valvular calcification that ranged from 23-83%. Overall, VC was demonstrated in 51-93% of the prevalent adult dialysis population and 47-83% of patients with CKD stages 3-5[9-15]. In the last 5 years, several additional studies have focused on VC assessment in earlier stages of CKD. In particular, one large observational study reported the CACS to be 2-fold higher in early CKD stages 1-3a (n=651) in comparison to a non-CKD cohort (n=3646; $p<0.001$)[16]. In addition, the presence of proteinuria among patients with CKD stage 3 was associated with a significantly higher prevalence of CACS at 22%[16].

Computed tomography (CT) - based techniques, including electron-beam CT (EBCT) and multi-slice spiral CT (MSCT), were regarded as the gold standard with high sensitivity (66-71%), specificity (78-91%) and negative predictive value when compared to coronary angiography[17, 18]. However, this tool lacks accuracy to detect the severity of stenotic plaques in patients with coronary artery disease[17]. In particular, one study of 140 prevalent

haemodialysis patients provided graded associations and the sensitivity and specificity of other diagnostic tests in comparison to CACS measured using EBCT[19]. Abdominal aortic calcification using lateral lumbar X-ray was shown to have good discriminatory value and correlation with moderate coronary artery calcification (CAC). The sensitivity and specificity of CACS and other simpler measure of VC are summarised in Table 1.

Table 1: Summary of diagnostic accuracy of several screening tools of vascular calcification.

Diagnostic Test	Sensitivity	Specificity	AUC	Reference Standard
CACS on EBCT[17, 18]	66-71	78-91	0.83[20]*	Coronary angiography
Lateral lumbar X-ray (AAC score of 7-24)[19]	67	91	0.78	CACS≥100
Echocardiogram (2 calcified valves)[19]	47	75	0.62	CACS≥100
Pulse pressure	51	54	0.51	CACS≥100

(quartile 4)[19]				

* AUC was 0.83 for stenosis >90%

AAC: abdominal aortic calcification; AUC: area under curve; CACS: coronary artery calcium score; EBCT: electron-beam computed tomography.

Lateral lumbar-X ray has been shown to be a reliable, accurate, simple and inexpensive measure of VC. The 2009 KDIGO CKD-MBD guidelines suggested that lateral lumbar X ray can be a reasonable alternative to CT-based techniques for VC assessment[9]. In addition, echocardiogram was also suggested as a screening tool for valvular calcification in the absence of CT-based techniques[9]. However, the level of evidence to support VC screening and utility of each measurement tool to provide additional CV risk stratification are weak (level 2C evidence). In addition, imaging modalities and scoring system for VC need to be standardised before regular screening can be widely recommended.

Over the last decade, several studies have focused on the impact of calcium and non-calcium based phosphate binders, vitamin D analogs and calcimimetics on CAC and mortality[21-26]. Recent meta-analyses suggests a survival benefit with the use of non-calcium based phosphate binders compared to calcium binders, however there are no substantial treatment effects to reduce the progression of VC among patients with CKD[27, 28].

Summary

To date, the literature strongly demonstrates the high prevalence of VC and the associations with poor survival among patients with CKD. There have also been major scientific advances relating to the multifaceted mechanisms of VC. *In vitro* studies have reported high

phosphate and calcium supplementation induced phenotypic changes and promoted calcification of vascular smooth muscle cells[29, 30].

Several imaging modalities including CACS, lateral lumbar X-ray and echocardiogram can be used to assess VC however scoring system needs to be refined and standardised. Therapeutic interventions using these methods have not consistently prevented or reduced VC in this cohort. In particular, the net CV benefits of non- calcium based phosphate binders over calcium-based phosphate binders and placebo needs to be evaluated using larger and well-designed randomised controlled trials with specific cost-effective analysis. Most therapeutic strategies on VC have focused on the dialysis population, whereas the opportunities for successful interventions are more likely to be found in earlier stages of CKD. A better understanding of the vascular biology at earlier stages of CKD with a view to seeking potential targeted therapies may be useful in reducing vascular burden in CKD. The KDIGO CKD-MBD working group has also published a recent update stating there was no new quality data on the available imaging modalities and there was insufficient evidence to justify routine screening for cardiovascular calcification in CKD patients[31]. Based on the current available literature, routine screening for VC is not indicated. However, modifiable risk factors such as lipid lowering therapy should be considered to reduce the overall atherosclerosis burden among patients with CKD.

References

1 Russo D, Palmiero G, De Blasio AP, Balletta MM, Andreucci VE. Coronary artery calcification in patients with CRF not undergoing dialysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2004; **44**: 1024-30.

2 Sigrist M, Bungay P, Taal MW, McIntyre CW. Vascular calcification and cardiovascular function in chronic kidney disease. *Nephrol Dial Transplant*. 2006; **21**: 707-14.

3 Palit S, Kendrick J. Vascular calcification in chronic kidney disease: role of disordered mineral metabolism. *Current pharmaceutical design*. 2014; **20**: 5829-33.

4 Giachelli CM. Vascular calcification mechanisms. *Journal of the American Society of Nephrology : JASN*. 2004; **15**: 2959-64.

5 Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK*, et al.* Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol*. 2002; **39**: 695-701.

6 Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int*. 2007; **71**: 438-41.

7 Panuccio V, Tripepi R, Tripepi G, Mallamaci F, Benedetto FA, Cataliotti A*, et al.* Heart valve calcifications, survival, and cardiovascular risk in hemodialysis patients. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2004; **43**: 479-84.

8 Rennenberg RJ, Kessels AG, Schurgers LJ, van Engelshoven JM, de Leeuw PW, Kroon AA. Vascular calcifications as a marker of increased cardiovascular risk: a meta-analysis. *Vascular health and risk management*. 2009; **5**: 185-97.

9 Kidney Disease: Improving Global Outcomes CKDMBDWG. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney international Supplement*. 2009: S1-130.

10 Honkanen E, Kauppila L, Wikstrom B, Rensma PL, Krzesinski JM, Aasarod K*, et al.* Abdominal aortic calcification in dialysis patients: results of the CORD study. *Nephrol Dial Transplant*. 2008; **23**: 4009-15.

11 Ix JH, Shlipak MG, Katz R, Budoff MJ, Shavelle DM, Probstfield JL*, et al.* Kidney function and aortic valve and mitral annular calcification in the Multi-Ethnic Study of Atherosclerosis (MESA). *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2007; **50**: 412-20.

12 Okuno S, Ishimura E, Kitatani K, Fujino Y, Kohno K, Maeno Y*, et al.* Presence of abdominal aortic calcification is significantly associated with all-cause and cardiovascular mortality in maintenance hemodialysis patients. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2007; **49**: 417-25.

13 Adeney KL, Siscovick DS, Ix JH, Seliger SL, Shlipak MG, Jenny NS*, et al.* Association of serum phosphate with vascular and valvular calcification in moderate CKD. *Journal of the American Society of Nephrology : JASN*. 2009; **20**: 381-7.

14 Wang AY, Wang M, Woo J, Lam CW, Li PK, Lui SF*, et al.* Cardiac valve calcification as an important predictor for all-cause mortality and cardiovascular mortality in long-term

peritoneal dialysis patients: a prospective study. *Journal of the American Society of Nephrology : JASN*. 2003; **14**: 159-68.

15 Sigrist MK, Taal MW, Bungay P, McIntyre CW. Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. *Clin J Am Soc Nephrol*. 2007; **2**: 1241-8.

16 Cho I, Min HS, Chun EJ, Park SK, Choi Y, Blumenthal RS*, et al.* Coronary atherosclerosis detected by coronary CT angiography in asymptomatic subjects with early chronic kidney disease. *Atherosclerosis*. 2010; **208**: 406-11.

17 Baumgart D, Schmermund A, Goerge G, Haude M, Ge J, Adamzik M*, et al.* Comparison of electron beam computed tomography with intracoronary ultrasound and coronary angiography for detection of coronary atherosclerosis. *J Am Coll Cardiol*. 1997; **30**: 57-64.

18 Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990; **15**: 827-32.

19 Bellasi A, Ferramosca E, Muntner P, Ratti C, Wildman RP, Block GA*, et al.* Correlation of simple imaging tests and coronary artery calcium measured by computed tomography in hemodialysis patients. *Kidney Int*. 2006; **70**: 1623-8.

20 Rumberger JA, Sheedy PF, Breen JF, Schwartz RS. Electron beam computed tomographic coronary calcium score cutpoints and severity of associated angiographic lumen stenosis. *J Am Coll Cardiol*. 1997; **29**: 1542-8.

21 Chertow GM, Burke SK, Raggi P, Treat to Goal Working G. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int*. 2002; **62**: 245-52.

22 Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A*, et al.* Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int*. 2005; **68**: 1815-24.

23 Qunibi W, Moustafa M, Muenz LR, He DY, Kessler PD, Diaz-Buxo JA*, et al.* A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2008; **51**: 952-65.

24 Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S*, et al.* The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney Int*. 2007; **72**: 1255-61.

25 Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K*, et al.* The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant*. 2011; **26**: 1327-39.

26 Chertow GM, Pupim LB, Block GA, Correa-Rotter R, Drueke TB, Floege J*, et al.* Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): rationale and design overview. *Clin J Am Soc Nephrol*. 2007; **2**: 898-905.

27 Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M*, et al.* Effect of calcium-based versus non-calcium-based phosphate binders on mortality in

patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet*. 2013; **382**: 1268-77.

28 Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM*, et al.* Effects of phosphate binders in moderate CKD. *Journal of the American Society of Nephrology : JASN*. 2012; **23**: 1407-15.

29 Chen NX, O'Neill KD, Duan D, Moe SM. Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. *Kidney Int*. 2002; **62**: 1724-31.

30 Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB*, et al.* Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. *Kidney Int*. 2002; **61**: 638-47.

31 Ketteler M, Elder GJ, Evenepoel P, Ix JH, Jamal SA, Lafage-Proust MH*, et al.* Revisiting KDIGO clinical practice guideline on chronic kidney disease-mineral and bone disorder: a commentary from a Kidney Disease: Improving Global Outcomes controversies conference. *Kidney Int*. 2015; **87**: 502-28.