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Coronary Artery Calcification (CAC) in Renal Dialysis Leads to Chronic Kidney Disease (CKD) - A Review

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Abstract

Vascular calcification is extremely prevalent in end-stage renal disease (ESRD) and independently predictive of subsequent cardiovascular events and mortality. Calcification can occur in both the intimal and medial layers of the vasculature, but medial calcification is that the major form in ESRD. Medial calcification rises large elastic artery stiffness and pulse-pressure, encourages left ventricular hypertrophy, lowers perfusion of the coronary arteries, and ultimately promotes increased cardiovascular mortality via increased risk of myocardial infarction and heart failure. Coronary artery calcification (CAC) develops early within the course of CKD and is related to mineral and bone disorders, which include but not limited to secondary hyperparathyroidism. In this review, recent data on the pathogenesis of Coronary artery calcification development and progression are discussed.

Keywords: Chronic Kidney Disease, Dialysis, Kidney Transplantation, Vascular Calcification, Coronary Artery Calcification, Coronary Artery Calcification Score

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Introduction

Cardiovascular mortality risk is elevated 5-10 fold in ESRD compared to the overall population [1]. A crucial risk factor for cardiovascular mortality in ESRD patients is vascular calcification, which is an abnormal deposition of calcium salts in plant tissue, including valves, blood vessels and therefore the heart [2,3]. Vascular calcification is very prevalent in ESRD patients, occurs decades before within the general population [4], and its progression accelerates dramatically once a patient initiates chronic dialysis [5] this is often of great clinical significance, because the presence and degree of calcification independently predicts future cardiovascular events, also as mortality [6,7]. The new era of research is related to the introduction of latest tools, allowing noninvasive, quantitative assessment of mineral depositions in soft tissues, and electron-beam computerized tomography (CT) and multi-slice CT (MSCT). A milestone study within the field was published in 1996 by Braun et al. [1] which documented a particularly high arteria coronaria calcium score (CACS) of 4290 ± 1509 Agatston units in patients on long-term hemodialysis (for comparison, a worth of 400 Agatston units is related to a particularly high risk of arteria coronaria disease during a general population [8].

Calcification can occur in both the intimal and medial layers of vasculature, but medial calcification is taken into account the more common and major sort of calcification in ESRD [2]. Intimal calcification is focal, related to inflammation, and is reflective of the degree of atherosclerosis within the aorta, coronary arteries and enormous vessels [9]. Medial calcification, also referred to as Monckeberg's sclerosis, occurs with aging, diabetes and chronic renal disorder (2), is characterized by diffuse mineral deposition throughout the vascular tree and is common within the muscular conduit arteries like the arteria femoralis [10]. It can occur independent of both atherosclerosis and an increased calcium and phosphorus serum concentration, and results from vascular smooth muscle fiber (VSMC) phenotypic changes promoting a upregulation of osteogenic programs [11]. Medial calcification occurs in young to middle-aged patients on chronic dialysis even in absence of traditional ardiovascular risk factors [12]. In fact, the extent of arteria coronaria calcification in dialysis patients is 2-5 fold greater in age- matched patients who have angiographically proven arteria coronaria disease [13]. Thus, non-traditional risk factors unique to the ESRD patients on chronic dialysis may predispose this population to accelerated vascular calcification [14].

Mechanisms Mediating Vascular Calcification in ESRD

Normal vessels and valve don't calcify, despite a serum

concentration of calcium and phosphorus at or above the solubility product [2], and calcification can still occur even with tight phosphate control [10]. Although vascular calcification was once considered to be a passive process of mineral deposition, high serum calcium and phosphorus concentration alone won't end in vascular calcification [15]. Instead, calcification is a lively cell-mediated process involving key regulators that are usually only involved in bone formation becoming expressed within the vasculature and promoting ossification [16]. While increased calcium and phosphate are not sufficient to promote vascular calcification, they are key to both the initiation and progression of calcification [15].

Although calcium and phosphate work synergistically to market vascular calcification, it's thought that calcium acts primarily by inducing apoptosis of VSMCs. This process promotes the release of membrane-bound matrix vesicles that act with the apoptotic VSMCS as nidus for further calcium and phosphate (hydoxyapatite deposition) [17] and promote further apoptosis [18]. Vessels from dialysis patients contain almost twice the calcium load of non-dialysis dependent chronic kidney disease patients, and are characterized by apoptotic VSMC damage and vesicle release (16). Increased VSMC apoptosis is observed even in pediatric dialysis patients, who are free from traditional cardiovascular risk factors [19]. Concurrent with VSMC apoptosis, phenotypic changes also occur in VSMCs.

VSMCs are mesenchymal in origin and thus can differentiate into other mesenchymalderived cells under conditions of stress [16]. Differentiation of contractile VSMCs into a chondroycte or osteoblast-like cells is key to vascular calcification and is promoted by active inducers. Ordinarily, key inhibitors counter this process, but this balance is shifted in ESRD (Figure 2). Active inducers that are likely up-regulated include bone morphogenic protein 2 (BMP-2), a key inducer of the differentiation of VSMCs to osetoblast-like cells, receptor activator of nuclear factor kappa B ligand (RANKL), a trans-membrane protein that promotes osteoclast differentiation and activation, and core binding factor alpha 1, runtrelated transcription factor 2 (CFBA1/RUNX2), an important transcription factor for osteoblast differentiation and osteogenesis [20]. Expression of osteochondrogenic genes is also increased even in arteries from pediatric dialysis patients [21].

These active inducers are ordinarily countered by active inhibitors of vascular calcification, which are down-regulated in ESRD. These include matrix gla protein, a transcription factors that inhibits VSMC differentiation to an osteoblast- like phenotype also as calcium crystal binding within the vascular matrix, osteopontin, a promoter of osteoclast function and inhibitor of hydroxyapatite crystal growth, fetuin-A, one among the foremost potent inhibitors of ectopic calcification and VSMC apoptosis, osteoprotegerin, an inhibitor of osteoclast differentiation, and BMP-7, a promoter of the VSMC phenotype [16]. Fetuin-A levels are low in patients on chronic dialysis and associate with increased coronary artery calcification and cardiovascular mortality [22].

Rodent models of insufficiency have demonstrated that the phenotypic change in VSMCs from a contractile to an osteochondrogenic phenotype, resulting from this shift in balance of active inhibitors and active promoters, requires high phosphate feeding [23]. Phosphate transport into cells is primarily mediated by sodium-dependent phosphate cotransporters, with PiT-1 being most important in VSMCs [2]. PiT-1 is required in vitro for differentiation to an osteochondrogenic phenotype and calcification to occur in human aortic smooth muscle cells [24]. In ESRD, pro-inflammatory cytokines and therefore the uremic milieu can increase PiT-1 expression in VSMCs, resulting in increased uptake of phosphorus albeit levels are still normal, and further promoting vascular calcification [25].

Conclusion

In summary, vascular calcification is extremely prevalent within the dialysis population and a significant contributor to the increased risk of cardiovascular mortality. It results not simply from a passive deposition of calcium and phosphate, but rather from active processes involving VSMC apoptosis, a shift within the balance of inhibitors and promoters, and VSMC differentiation from a contractile to osteochondrogenic phenotype. Although many risk factors of the event and progression of arterial calcification were identified, they're not universally confirmed across studies; only age seems to work out CAC altogether studies and baseline CAC usually determines its progression over time. The extremely complex nature of uremic toxicity, additionally complicated by treatment (dialysis or transplantation), makes the identification of one or main modifiable risk factor extremely difficult. Future research is required to work out if targeting these processes can ultimately reduce vascular calcification during this high cardiovascular risk population.

References

1. Foley RN, Parfrey PS (2010) Cardiovascular disease and mortality in ESRD. J nephrology 11: 239-245.
2. Giachelli CM (2012) The emerging role of phosphate in vascular calcification. Kidney Int 75: 890-897.
3. Verberckmoes SC, Persy V, Behets GJ, Neven E, Hufkens A, et al. (2007) Uremia-related vascular calcification: more than apatite deposition. Kidney Int 71: 298- 303.
4. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, et al. (2010) Coronary-artery calcification in young adults with endstage renal disease who are undergoing dialysis. The New England Journal of Medicine 342: 1478-1483.
5. Foley RN, Parfrey PS, Sarnak MJ (2015) Clinical epidemiology of cardiovascular disease in chronic renal disease. American journal of kidney diseases: the official journal of the National Kidney Foundation 32: S112-119.
6. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM (2011) Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension 38: 938-942.
7. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, et al. (2013) Arterial media calcification in end- stage renal disease: impact on all-cause and cardiovascular mortality. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 18: 1731-1740.
8. Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, et al. (2016) Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. Am J Kidney Dis 27: 394-401.

9. Abedin M, Tintut Y, Demer LL (2014) Vascular calcification: mechanisms and clinical ramifications. Arteriosclerosis, thrombosis, and vascular biology 24: 1161-1170.

10. Covic A, Kanbay M, Voroneanu L (2010) Vascular calcification in chronic kidney disease. Clinical science 119: 111-121.

11. Hruska KA, Saab G, Mathew S, Lund R (2014) Renal osteodystrophy, phosphate homeostasis, and vascular calcification. Seminars in dialysis 20: 309-315.

12. Toussaint ND, Kerr PG (2007) Vascular calcification and arterial stiffness in chronic kidney disease: implications and management. Nephrology 12: 500-509.

13. Moe SM, Chen NX (2014) Pathophysiology of vascular calcification in chronic kidney disease. Circulation research 95: 560-567.

14. Kendrick J, Chonchol M (2011) The role of phosphorus in the development and progression of vascular calcification. American journal of kidney diseases: the official journal of the National Kidney Foundation 58: 826-834.

15. Shroff R, Long DA, Shanahan C (2013) Mechanistic insights into vascular calcification in CKD. Journal of the American Society of Nephrology: JASN 24: 179-189.

16. Mizobuchi M, Towler D, Slatopolsky E (2009) Vascular calcification: the killer of patients with chronic kidney disease. Journal of the American Society of Nephrology: JASN 20: 1453-1464.

17. Olszak IT, Poznansky MC, Evans RH, Olsan D (2010) Extracellular calcium elicits a chemokinetic response from monocytes in vitro and in vivo. The Journal of clinical investigation 105: 1299-1305.

18. Shroff RC, McNair R, Figg N, Skepper JN (2008) Dialysis accelerates medial vascular calcification in part by triggering smooth muscle cell apoptosis. Circulation 118: 1748-1757.

19. Ketteler M, Bongartz P, Westenfeld R, Wildberger JE, Mahnken AH, et al. (2013) Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. Lancet 361: 827-833.

20. El-Abbadi MM, Pai AS, Leaf EM, Yang HY, Bartley BA, et al. (2009) Phosphate feeding induces arterial medial calcification in uremic mice: role of serum phosphorus, fibroblast growth factor-23, and osteopontin. Kidney international 75: 1297-1307.

21. Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM (2011) Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circulation Research 109: 697-711.

22. Juppner H (2007) Novel regulators of phosphate homeostasis and bone metabolism. Ther Apher Dial 11: S3-S22.

23. Wolf M, Molnar MZ, Amaral AP, Czira ME, Rudas A, et al. (2011) Elevated fibroblast growth factor 23 is a risk factor for kidney transplant loss and mortality. J Am Soc Nephrol 22: 956-966.

24. Nakano C, Hamano T, Fujii N, Matsui I, Tomida K, et al. (2012) Combined use of vitamin D status and FGF23 for risk stratification of renal outcome. Clin J Am Soc Nephrol 7: 810-819.

25. Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, et al. (2011) Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 79: 1370-1378.