Imaging Cardiovascular in Chronic Kidney Disease

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Chronic kidney disease (CKD) patients have a higher risk of developing early cardiovascular disease (CVD). Although vascular calcification (VC) is one of the strongest predictors of CVD risk, its diagnosis among the CKD population remains a serious clinical challenge. Imaging methods, henceforward referred to as imaging biomarkers, have played a crucial role in the diagnosis of VC, with important insights into cardiovascular risk. One of the reasons that may explain the struggle for accurate VC diagnosis in CKD patients is that the calcification characteristics change alongside renal deterioration and CKD progression. Novel circulating biomarkers like Fetuin-a, Matrix Gla Protein (MGP) and Gla Rich Protein (GRP), representing a more direct and unique reflection of the molecular dynamics involved in VC mechanisms, could complement VC clinical diagnostic and add value to patient care.

Keywords: chronic kidney disease ; vascular calcification ; biomarkers

1. Radiology Techniques

Conventional X-rays can identify extra-skeletal calcifications, particularly in the aorta and peripheral arteries. Radiographs have the advantage of being economical, with less exposure to radiation compared to CT scans. They seem to provide valid prognostic information scores, as well as simple and readily available clinical data, representing a good method to screen for the presence of vascular calcification (VC) in Chronic kidney disease (CKD) patients. The KDIGO (kidney disease: improving global outcomes) guidelines from 2017 [1] recommend radiologic methods as evaluation tools for VC diagnosis, particularly the lateral lumbar spine X-ray for VC assessment in stages 3–5 D. In concordance, several observational studies involving CKD populations have confirmed that using plain X-rays in different body locations is an effective alternative for VC detection and CVD risk evaluation, either in early stages of the disease [2] or in a hemodialysis population [3].

Similar to ultrasonography and computed tomography, plain X-rays also have specific scoring tools that can give physicians a semi-quantitative analysis of calcium deposits. In 2004, Teresa Adragão et al. developed a simple score to assess subclinical vascular disease in a prospective observational study involving 123 hemodialysis patients [4]. The Adragão score, obtained by a plain X-ray of the hands and pelvis (iliac, femoral, radial and digital arteries), is not only a tool for the assessment of cardiovascular risk, but also an indicator associated with arterial stiffness and mortality in dialysis patients [5]. The Adragão score is suitable for detection of heavy deposits of mineral crystals in the media layer of the vessels; the most common type of calcification affecting small vessels and typically found among CKD patients. These deposits localized in peripheric arteries are recognized to have a high CVD risk prognostic value for CKD patients [6]. Another X-ray-based score was established by Kauppila et al. [7] from a retrospective study involving 617 lateral lumbar radiographs performed on patients from the Framingham heart study. The Kauppila score, representing the abdominal aorta calcification score (AACS) [8], assesses vascular calcifications via lateral abdominal X-rays and was proven to be a simple, low cost assessment of subclinical vascular disease. More recently, it was correlated with cardiovascular event prediction in a study involving 187 peritoneal dialysis patients, and was showed to improve risk stratification beyond the Framingham risk score in another study involving 184 hemodialysis patients [9]. Observational studies comparing the performance of both the Adragão and Kauppila scores with the CT-scan based score (Agatston) support the notion that X-ray-based calcification scores are valid alternatives to CT scans, with incremental prognostic values for CV events beyond traditional risk factors. One of the studies, involving 143 patients at various stages of CKD, showed a significant and linear relationship between the Agatston and Kaupilla scores [10]. In addition, a cross-sectional study performed in 50 hemodialysis patients showed a correlation between the Adragao and Agatston scores to clinically detect vascular calcification for this population [11].

Nevertheless, X-ray imaging techniques still include drawbacks and limitations, such as they allow a clear identification of VC lesions only when the vessel is considerably calcified [12]; difficulties in distinguishing between medial and intimal calcification if they coexist in the vessel; the semi-quantitative nature of the calcification reading due to the inability to

precisely quantify calcium deposits; and the inability to reliably detect subtle temporal changes in VC. These pose major challenges for early VC diagnosis and disease progression monitoring, limiting its use for CVD risk detection in early stages of CKD—stages 1 and 2, where the disease is in most cases silent—highlighting a clear need for complementary clinical exams.

2. Ultrasonography Techniques

In conventional ultrasonography methods, their resolution is dependent on the depth of area, which makes them appropriate for detection of calcification deposits in superficial arteries (carotid, femoral and peripheral arteries). Ultrasonography has the benefit of no radiation exposure and is a relatively economical choice, widely available at most health care facilities, and has the potential to be implemented as a routine method for VC detection. Since it specifically analyzes the wall thickness and lumen size, it can detect stenosis of the arteries and mineral deposition sites either in vessels or cardiac valves [9][10]. Some studies have suggested the more efficient ability of ultrasonography to detect medial calcification compared to the X-ray approach [12], by it clearly being able to distinguish between the different layers of the arterial wall, with the advantage of also detecting calcium deposits in aortic and mitral valves. Since medial calcification is prevalent in CKD patients, ultrasonography, and its associated VC scores, appears to be a good method to assess VC in the CKD population [12][13][14][15].

Several calcification scores based on ultrasound detection of calcium deposits have showed the potential of this technique to detect VC in early or even asymptomatic CVD patients at risk. Although not yet deeply studied in the CKD population, some of these scores can be particularly relevant for CKD at earlier stages where CVD diagnostic is particularly challenging [16][17]. The transthoracic echocardiography-based score (Echo score) [18] showed strong correlation with coronary artery disease (CAD) and association with the CT-scan based score (Agatston) in non CKD patients with low/intermediate CVD risk [19]. The color Doppler ultrasound score (CALCs) [20] was found to be highly correlated with markers of subclinical atherosclerosis, such as the intima–media thickness and arterial stiffness in asymptomatic patients at low–intermediate CVD risk, predicting CVD events beyond the traditional risk factors [21]. The duplex ultrasound (DUS)-based score, named DULLAC, assessed the lower limbs artery calcification of six patients selected randomly from the Vascular Studies Unit at Cambridge University Hospitals and added an input to risk stratification in non-CKD patients with peripheral arterial disease [22] by correlating with CT-based arterial calcium measurements.

More recently, intravascular modality based on wave-sound, called intravascular ultrasound (IVUS), has revolutionized ultrasonography methods by detailing plaque and vessel wall in real-time throughout the coronary artery tree. IVUS has been largely used due to its sensitivity and specificity for detecting calcium within a plaque, enabling calcium deposit localization and distribution, as well as a more precise quantification of calcification than the previous described ultrasound techniques [23]. A study comprising 440 patients with stable angina aimed to compare IVUS, optical coherence tomography (OCT) and coronary angiography in their ability to target lesion calcification in patients undergoing percutaneous coronary intervention. The results showed that calcium deposits were detected by IVUS in 83% of patients, OCT in 77% of patients and angiography in 40% of patients, revealing a higher accuracy of the IVUS method in detecting calcifications. This ultrasound modality score [23], designated as the IVUS calcium score, was proposed as a robust and accurate tool to assess both the presence and amount of coronary calcification.

Although promising for predicting CVD risk, these ultrasonography scores still lack specific evidence for CKD patients, requiring further studies to validate its use for routine assessment among this population. Additionally, due to its invasive nature, the IVUS method should be used with precaution to avoid disturbance of existing unstable plaques.

Even though ultrasonography can add substantial input to VC diagnosis, it still reflects some limitations regarding evaluation of calcium mineral deposition. Current ultrasonography methods, except for IVUS, lack on providing a quantification of mineral deposits in vessels and valves [24]. Furthermore, these ultrasonography techniques still fail on providing detection of microcalcifications in atheromatous plaques, and are fit only for diagnosis of macrocalcifications.

3. Molecular Imaging Techniques

Computed tomography (CT) scanning is the gold standard method for evaluation of VC, allowing an objective quantification of calcium deposits. CT scanning is a non-invasive exam using X-rays for imaging of the heart and its structures.

Computed tomography is very useful for cardiovascular risk stratification by providing a reliable quantification of macroscopic calcium deposits expressed as a clinical coronary artery calcium score (CACS) [25] or aortic valve

calcification score (AVCS) [26]. The importance of CACS evaluation is evidenced by the latest 2019 guidelines of the American College of Cardiology/American Heart Association, which included for the first time “Coronary Artery Calcium” as an assessment tool for cardiovascular risk in individuals with intermediate predicted risk [27]. CACSs to stratify the cardiovascular risk of their patients, and monitor disease progression: (1) the Agatston score [28], (2) volume of calcium score [29] and (3) calcium mass score [30]. Mostly due to its simplicity, the score proposed by the cardiologist Arthur Agatston in 1990 continues to be the reference CACS used for most population-based studies involving CVD risk stratification. These CAC-based scores can be used to detect calcification not only in carotids arteries, but also in larger arteries such as the abdominal [27][28] or thoracic aorta [31], and even in cardiac valves [32].

In addition, large cohort studies [31][33][34] have demonstrated the ability of CACS to predict cardiac events in asymptomatic subjects, supporting an increment value over conventional risk factor assessment. In a CKD scenario, the extent of vascular and valvular calcification increases with renal deterioration throughout the disease stage progression. These CT scoring tools become important because the information provided by CAC score assessment can significantly alter clinical decisions, providing a closer disease monitoring with the possibility to intervene to delay VC progression [35] [36][37]. In a large study of CKD patients as part of the Chronic Renal Insufficiency Cohort trial, the Agatston score was evaluated in 1541 CKD patients from stage two to four without established CVD [38]. In these patients, the CAC score was shown to improve risk prediction for cardiovascular disease, myocardial infarction and heart failure relative to established cardiovascular disease risk factors, highlighting the clinical input that the CAC score can add to medical care.

However, CT scans cannot accurately differentiate between the intimal and medial location of calcium deposits due to low resolution captured by the scan, challenging the detection of medial calcification in small arteries, which is characteristic in CKD. Moreover, the high equipment cost, the high-dose ionizing radiation exposure, the risk of nephropathy due to the contrast agent when coupled with angiography and the inability to perform in-office testing add unfavorable circumstances for the regular use of this method to assess VC, particularly in renal disease patients. Additionally, medial artery calcification does not always develop proportionally to obstructive coronary artery disease (CAD), limiting the prognostic value of CT scanning coupled with angiography [39]. Another major disadvantage of CT scans is that they only provide quantification of macrocalcifications. Although CT scans are considered good markers of overall CVD burdens, their inability to detect microcalcifications also argues their use in identifying vulnerable lesions prone to rupture, often characterized by the presence of microcalcifications in early phases of VC development.

Recently, other molecular imaging techniques have been explored as an alternative to CT scans, aiming to explore this flaw of lack of detection of microcalcifications. In CKD, a continuum of calcification typically occurs with evidence of both micro- and macro-calcification in the intima and media. However, X-rays, ultrasonography (except for IVUS) and CT-scans can only detect macrocalcifications. A solution for detecting microcalcification is reported in a recent technique called positron emission tomography (PET). This remarkable tool uses a radioactive tracer ((18) F-NaF) to detect small calcium deposits on the endothelium surface. A deeper description of the method can be found elsewhere. The use of PET fosters new approaches for diagnosis of microcalcification in the vascular tree, adding a clinical possibility to distinguish between areas of macro- and micro-calcification [40]. However, this technique is not yet commonly applied for clinical monitoring of cardiovascular disease in CKD patients, being mostly used for microcalcification diagnosis for several forms of cancer or for CVD in general [41].

Overall, due to the lack of sensitivity in distinguishing between calcification of the intima and media layers and limitations in detecting microcalcifications, CT scans might not always be the best method to assess VC in a CKD context. In light of these limitations, radiology and ultrasonography methods, under some circumstances, might be preferable choices over CT scans for CVD risk stratification in early CKD stages. However, they also have considerable restrictions for cardiovascular risk prediction in CKD patients. The establishment of a multimodality-based diagnostic tool, using not only imaging but also circulating markers for VC, could overcome the individual gaps of each imaging technique. The possibility to integrate novel VC circulating biomarkers in this multimodality-based diagnostic approach, could not only reduce the medical exam cost burden, but also introduce complementary information on VC pathophysiological pathways with implications for the disease management. Novel circulating biomarkers like Fetuin-a, Matrix Gla Protein and Gla Rich Protein, representing a more direct and unique reflection of the molecular dynamics involved in VC mechanisms, could complement VC clinical diagnostic and add value to patient care

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