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Review

Cardiovascular calcifications in chronic kidney disease: Potential therapeutic implications☆

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ABSTRACT

Cardiovascular (CV) calcification is a highly prevalent condition at all stages of chronic kidney disease (CKD) and is directly associated with increased CV and global morbidity and mortality. In the first part of this review, we have shown that CV calcifications represent an important part of the CKD–MBD complex and are a superior predictor of clinical outcomes in our patients. However, it is also necessary to demonstrate that CV calcification is a modifiable risk factor including the possibility of decreasing (or at least not aggravating) its progression with iatrogenic manoeuvres. Although, strictly speaking, only circumstantial evidence is available, it is known that certain drugs may modify the progression of CV calcifications, even though a direct causal link with improved survival has not been demonstrated. For example, non-calcium-based phosphate binders demonstrated the ability to attenuate the progression of CV calcification compared with the liberal use of calcium-based phosphate binders in several randomised clinical trials. Moreover, although only in experimental conditions, selective activators of the vitamin D receptor seem to have a wider therapeutic margin against CV calcification. Finally, calcimimetics seem to attenuate the progression of CV calcification in dialysis patients. While new therapeutic strategies are being developed (i.e. vitamin K, SNF472, etc.), we suggest that the evaluation of CV calcifications could be a diagnostic tool used by nephrologists to personalise their therapeutic decisions.

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Calcificaciones cardiovasculares en la enfermedad renal crónica: Potenciales implicaciones terapéuticas

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RESUMEN

La calcificación cardiovascular (CV) es una condición muy prevalente en todos los estadios de la enfermedad renal crónica (ERC) y se asocia directamente a una mayor morbimortalidad CV y global. En la primera parte de esta revisión hemos mostrado cómo las calcificaciones CV son una característica destacada del complejo CKD-MBD (*chronic kidney disease-mineral and bone disorders*) así como un predictor superior de la evolución clínica de nuestros pacientes. No obstante, es necesario también demostrar que la calcificación CV es un factor de riesgo modificable y con la posibilidad, como mínimo, de poder disminuir su progresión (o al menos no agravarla) con maniobras iatrogénicas. Aunque estrictamente solo se disponga de evidencias circunstanciales, sabemos que el uso de determinados fármacos puede modificar la progresión de las calcificaciones CV, aunque no se ha demostrado un vínculo directo causal sobre la mejoría de la supervivencia. En este sentido, el uso de quelantes del fósforo no cálcicos ha demostrado reducir la progresión de las calcificaciones CV en comparación con el uso liberal de quelantes cálcicos en varios ensayos clínicos aleatorizados. Por otra parte, aunque solo a nivel experimental, los activadores selectivos del receptor de la vitamina D parecen mostrar un mayor margen terapéutico contra la calcificación CV. Finalmente, los calcimiméticos también parece que podrían atenuar la progresión de la calcificación CV en pacientes en diálisis. Mientras se desarrollan nuevas estrategias terapéuticas (p. ej. vitamina K, SNF472...), proponemos que la valoración de las calcificaciones CV puede ser una herramienta usada por el nefrólogo para la toma individualizada de decisiones terapéuticas.

Introduction

Presently, it is widely accepted that chronic kidney disease (CKD) is an independent cardiovascular (CV) risk factor and that its mortality rate increases exponentially as kidney function progressively deteriorates.[1] In this context, we have previously described the types of CV calcification,[2,3] its association with CV events, mortality,[2] and why we justify assessing vascular calcification in routine nephrology clinical practice.[2] Nonetheless, it is important to demonstrate beforehand that CV calcification is also a modifiable risk factor with at least the possibility of decreasing its progression and not aggravating it in the case of not being able to reverse it. Then, the objective of the second part of this review, is to explain how CV calcification is a modifiable risk factor despite being a late and secondary phenomenon and only circumstancial evidence available.[4–6] Certainly CV calcification is a risk factor that, unfortunately, we may contribute to by adding unwanted iatrogenic effects.[6–9]

Controlling traditional cardiovascular risk factors and vascular calcification

Observational studies have shown that the differential use of drugs acting on the CV system such as statins, β-blockers, calcium channel antagonists, and angiotensin-converting enzyme (ACE) inhibitors/angiotensin-II-receptor blockers (ARB) are associated with a lower risk of CV events and death in CKD patients.[10] However, there is no single drug that clearly demonstrates an improvement in survival in dialysis patients.[11] The treatment of CV risk factors for atherosclerosis, such as hyperlipidaemia, does not improve the survival of these patients,[12,13] and only the reduction of LDL cholesterol with simvastatin plus ezetimibe decreased the incidence of CV events in a wide range of advanced CKD patients, but without demonstrating a benefit in overall survival.[14] Treating hyperlipidaemia with statins has also failed to reduce vascular calcification.[15,16] Only one recent meta-analysis has indicated that using statins is effective in the primary prevention of CV disease in CKD.[17] Moreover, there are very limited or non-existent data available on the effect of control of diabetes and blood pressure, as well as quitting tobacco on vascular calcification or the CV risk in the CKD population.[18] Only in new experimental models, ARBs have been demonstrated to have powerful protective effects on vascular calcification by interrupting vascular osteogenesis. The combination of statins and ARBs produces potent synergistic protective effects against vascular calcification in CKD that is beyond the control of blood pressure.[19–22]

Control of CKD–MBD and vascular calcification-related risk factors

Many CKD–MBD-related treatments, such as phosphate (P) binders, vitamin D derivatives, calcimimetics, and others, have been widely demonstrated to influence on