

REVIEW

Relevance of ultrasound detection and assessment of vascular calcifications in chronic kidney disease

Relevancia de la detección y evaluación de calcificaciones vasculares mediante ecografía en la enfermedad renal crónica

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ABSTRACT

Introduction: chronic kidney disease (CKD) affects approximately 10 % of the Spanish population and constitutes an independent cardiovascular risk factor. Vascular calcifications, especially in the abdominal aorta, are significantly associated with increased cardiovascular mortality in patients with CKD. This systematic review evaluates the evidence on the usefulness of ultrasound to detect and assess vascular calcifications in patients with CKD, and its relevance as a cardiovascular risk factor.

Method: a systematic search of multiple electronic databases was conducted until July 2024. Original studies published between 2000 and 2024 evaluating the use of ultrasound to detect vascular calcifications in adult patients with CKD at any stage were included. Reviews, letters, editorials, animal studies and those not published in English or Spanish were excluded. Methodological quality was assessed using the Newcastle-Ottawa scale for observational studies and the Cochrane tool for clinical trials.

Results: twenty-eight studies were included with a total of 50 to 3 000 participants per study. Most were observational studies, with 3 randomised clinical trials. Ultrasound showed good correlation with computed tomography ($r=0,65-0,82$) to quantify aortic and femoral calcifications. The presence of aortic calcifications was associated with increased risk of cardiovascular mortality (HR 1,8-3,2) in patients with advanced CKD and on haemodialysis. Iliac/femoral calcifications were associated with increased risk of cardiovascular events (RR 1,6-2,4) in patients with stage 3-5 CKD. Incorporation of ultrasound assessment of calcifications into CKD-specific risk algorithms significantly improved their predictive performance.

Discussion: ultrasonography emerges as a valuable tool for the detection of vascular calcifications due to its non-invasive nature, low cost and ability to perform repeated assessments. However, limitations such as heterogeneity in assessment methods, variable sample sizes and lack of long-term follow-up in some studies were identified. Further research is needed to standardise protocols and assess the long-term impact of interventions based on ultrasound detection of calcifications.

Conclusions: ultrasonography is an effective and accessible tool for detecting and assessing vascular calcifications in patients with CKD, providing relevant prognostic information for cardiovascular risk

stratification. Its consideration as a first-line tool in nephrological practice is recommended. However, large-scale prospective studies are needed to definitively validate its prognostic value in different stages of CKD and to evaluate the efficacy of early interventions based on these findings.

Keywords: Vascular Calcification; Chronic Kidney Disease; Ultrasound; Cardiovascular Risk; Systematic Review.

RESUMEN

Introducción: la enfermedad renal crónica (ERC) afecta aproximadamente al 10 % de la población española y constituye un factor de riesgo cardiovascular independiente. Las calcificaciones vasculares, especialmente en la aorta abdominal, se asocian significativamente con un aumento de la mortalidad cardiovascular en pacientes con ERC. Esta revisión sistemática evalúa la evidencia sobre la utilidad de la ecografía para detectar y evaluar calcificaciones vasculares en pacientes con ERC, y su relevancia como factor de riesgo cardiovascular.

Método: se realizó una búsqueda sistemática en múltiples bases de datos electrónicas hasta julio de 2024. Se incluyeron estudios originales publicados entre 2000 y 2024 que evaluaran el uso de ecografía para detectar calcificaciones vasculares en pacientes adultos con ERC en cualquier estadio. Se excluyeron revisiones, cartas, editoriales, estudios en animales y aquellos no publicados en inglés o español. La calidad metodológica se evaluó utilizando la escala de Newcastle-Ottawa para estudios observacionales y la herramienta Cochrane para ensayos clínicos.

Resultados: se incluyeron 28 estudios con un total de 50 a 3 000 participantes por estudio. La mayoría fueron estudios observacionales, con 3 ensayos clínicos aleatorizados. La ecografía mostró buena correlación con tomografía computarizada ($r=0,65-0,82$) para cuantificar calcificaciones aórticas y femorales. La presencia de calcificaciones aórticas se asoció con mayor riesgo de mortalidad cardiovascular (HR 1,8-3,2) en pacientes con ERC avanzada y en hemodiálisis. Las calcificaciones ilíacas/femorales se asociaron con mayor riesgo de eventos cardiovasculares (RR 1,6-2,4) en pacientes con ERC estadios 3-5. La incorporación de la evaluación de calcificaciones por ecografía en algoritmos de riesgo específicos para ERC mejoró significativamente su rendimiento predictivo.

Discusión: la ecografía emerge como una herramienta valiosa para la detección de calcificaciones vasculares debido a su naturaleza no invasiva, bajo costo y capacidad para realizar evaluaciones repetidas. Sin embargo, se identificaron limitaciones como la heterogeneidad en los métodos de evaluación, tamaños de muestra variables y falta de seguimiento a largo plazo en algunos estudios. Se requiere más investigación para estandarizar protocolos y evaluar el impacto a largo plazo de intervenciones basadas en la detección ecográfica de calcificaciones.

Conclusiones: la ecografía es una herramienta efectiva y accesible para detectar y evaluar calcificaciones vasculares en pacientes con ERC, proporcionando información pronóstica relevante para la estratificación del riesgo cardiovascular. Se recomienda su consideración como herramienta de primera línea en la práctica nefrológica. Sin embargo, se necesitan estudios prospectivos a gran escala para validar definitivamente su valor pronóstico en diferentes estadios de ERC y evaluar la eficacia de intervenciones tempranas basadas en estos hallazgos.

Palabras Clave: Calcificación Vascular; Enfermedad Renal Crónica; Ecografía; Riesgo Cardiovascular; Revisión Sistemática.

INTRODUCTION

Chronic kidney disease (CKD) is a significant public health problem worldwide, affecting approximately 10 % of the Spanish population and constituting an independent cardiovascular risk factor.^(1,2) In the Americas, kidney disease is among the leading causes of mortality and disease burden, ranking eighth in overall mortality in 2019.⁽³⁾ The situation is particularly worrying in countries such as Nicaragua, El Salvador, and Bolivia, which have the highest mortality rates from kidney disease in the region.^(3,4)

Vascular calcifications, especially in the abdominal aorta (AAA), have been significantly associated with increased cardiovascular and all-cause mortality in hemodialysis patients.^(5,6) Several studies have shown that indices such as aortic calcification area (ACA) and aortic pulse wave velocity (PWV) are useful predictors of adverse outcomes and long-term mortality in these patients.^(7,8,9)

Traditionally, vascular calcification has been assessed using X-ray-based techniques such as plain radiography or computed tomography. However, these techniques have limitations, such as radiation exposure and the inability to determine the exact location of calcium in the arterial wall. In this context, Ultrasound emerges as a promising alternative for detecting and evaluating vascular calcifications, offering advantages such as the

absence of radiation, lower cost, and the possibility of performing repeated studies in short periods.

Vascular calcifications represent an important cardiovascular risk factor in patients with chronic kidney disease (CKD), being associated with increased morbidity and mortality in this population.^(1,2) Timely detection and assessment of these calcifications allow for better risk stratification and guide early therapeutic interventions.⁽³⁾ Various imaging methods have been used to identify vascular calcifications, including computed tomography, plain radiography, and Ultrasound.^(4,5) Ultrasound has advantages such as low cost, absence of ionizing radiation, and wide availability, which position it as a potentially helpful tool for screening and monitoring vascular calcifications in patients with CKD.⁽⁶⁾

However, there is still no consensus on the specific role of Ultrasound in detecting and evaluating vascular calcifications in the context of CKD. Aspects such as its diagnostic accuracy, standardized evaluation protocols, and its impact on clinical management and patient prognosis require further investigation.

The objective of this review is to analyze the available evidence on the use of Ultrasound for the detection and evaluation of vascular calcifications in patients with CKD, explicitly addressing the following questions:

1. What is the diagnostic accuracy of Ultrasound in identifying vascular calcifications in patients with CKD compared to other imaging methods?
2. What ultrasound protocols or techniques have been proposed for evaluating vascular calcifications in CKD, and what is their clinical applicability?
3. What impact does ultrasound detection of vascular calcifications have on cardiovascular risk stratification and clinical management of patients with CKD?
4. What are the advantages and limitations of Ultrasound compared to other methods for evaluating vascular calcifications in the context of CKD?

To address these questions, a literature review was conducted, including original studies published between 2000 and 2024 that evaluated the use of Ultrasound to detect vascular calcifications in adult patients with CKD at any stage. The search was conducted in multiple electronic databases, and 28 studies that met the eligibility criteria were included, covering a variety of study designs and geographical contexts.

This review aims to provide an updated synthesis of the evidence to guide the appropriate use of Ultrasound in clinical practice for detecting and monitoring vascular calcifications in patients with CKD and to identify areas requiring further research.

METHOD

Selection of studies

The initial search of electronic databases identified 245 potentially relevant records. After removing duplicates, 183 titles and abstracts were reviewed. Of these, 62 articles were selected for full-text review. Finally, 28 studies were included that met the eligibility criteria.

Characteristics of the studies included

The 28 studies included were published between 2000 and 2024, with a notable increase in the last decade, reflecting the growing interest in this topic. Most were observational studies (20 prospective cohort studies, 5 cross-sectional studies) and 3 randomized clinical trials. The sample size ranged from 50 to 3,000 participants, with a median of 250 patients. All studies included adult patients with chronic kidney disease at different stages, including patients on hemodialysis. The duration of follow-up in longitudinal studies ranged from 1 to 10 years, with a median of 4 years.

The studies were conducted in diverse geographical settings: 12 in Europe, 8 in North America, 5 in Asia, and 3 multinational studies. This geographical diversity increases the generalizability of the results. The methodological quality of the studies was variable, with 18 studies considered high quality (NOS score ≥ 7 or low risk of bias according to Cochrane) and 10 of moderate quality.

Original studies published between 2000 and 2024 that evaluated the use of ultrasound to detect vascular calcifications in adult patients (≥ 18 years) with chronic kidney disease (CKD) at any stage were included. Reviews, letters, editorials, animal studies, and those not published in English or Spanish were excluded.

Electronic databases were searched from inception to July 5, 2024: MEDLINE (via PubMed), Embase, Cochrane Library, Web of Science, SciELO, Scopus, Google Scholar, and ClinicalKeys services. Reference lists of included articles and relevant reviews were also reviewed.

The following search strategy was used in MEDLINE (adapted for other databases):

((("Renal Insufficiency, Chronic" [Mesh] OR "chronic kidney disease"[tiab] OR "CKD"[tiab]) AND ("Vascular Calcification"[Mesh] OR "vascular calcification"[tiab] OR "arterial calcification"[tiab])) AND ("Ultrasonography"[Mesh] OR "ultrasound"[tiab] OR "sonography"[tiab] OR "echography"[tiab]))

DEVELOPMENT

Vascular calcification assessment

Methods for assessing vascular calcification using ultrasound varied between studies, reflecting the lack of a standardized protocol:

- 18 studies evaluated calcifications in the abdominal aorta
- 12 studies evaluated calcifications in the iliac and femoral arteries
- 8 studies evaluated carotid calcifications.

Some studies evaluated multiple vascular territories, allowing for a more comprehensive assessment of the calcification process. Most studies (22/28) used B-mode ultrasound to identify and quantify calcifications. Six studies supplemented this with Doppler assessment, which allowed for evaluation of the hemodynamic implications of calcifications.

The most commonly used scoring systems were:

- Kauppila index for aortic calcifications (10 studies): This index assesses the presence and extent of calcifications in the abdominal aorta, with scores ranging from 0 to 24.
- Adragao score for iliac/femoral calcifications (8 studies): This system assesses the presence of calcifications in 4 vascular territories, with scores ranging from 0 to 8.
- Carotid intima-media thickness (6 studies): Although not specific for calcifications, it was used as a surrogate marker for atherosclerosis.

Four studies proposed new scoring systems, but these still require external validation.

Association with cardiovascular risk

Twenty-three studies evaluated the association between vascular calcifications detected by ultrasound and cardiovascular events or mortality. The main findings were:

- The presence of aortic calcifications was associated with an increased risk of cardiovascular mortality (HR 1,8-3,2) in patients with advanced CKD and on hemodialysis.^(11,12) This association was independent of traditional risk factors and stronger in younger patients.
- Iliac/femoral calcifications were associated with an increased risk of cardiovascular events (RR 1,6-2,4) in patients with stage 3-5 CKD. The association was stronger for peripheral ischemic events.^(13,14)
- Carotid intima-media thickness >0,9 mm was associated with a higher risk of coronary events (OR 1,7-2,5) in patients with CKD.^(15,16) This association was stronger in patients with concomitant albuminuria.
- The progression of calcifications assessed by ultrasound was associated with worse cardiovascular prognosis (HR 1,4-2,1 per increase in score). This underscores the importance of serial assessment.^(17,18)

Three studies found that the association between calcifications and cardiovascular events was stronger in patients with CKD than in the general population, suggesting an interaction between renal dysfunction and the vascular calcification process.

Comparison with other diagnostic methods

Eight studies compared ultrasound with other methods for assessing calcifications:

- Ultrasound showed good correlation with computed tomography ($r=0,65-0,82$) for quantifying aortic and femoral calcifications.^(19,20,21,22) However, CT was superior for detecting small or deep calcifications.
- Ultrasound had higher sensitivity than plain radiography for detecting initial calcifications in medium-sized arteries.^(23,24) This is relevant for early detection in patients with early CKD.
- Ultrasound allowed dynamic assessment of arterial stiffness, complementary to coronary calcium quantification by CT.^(25,26) This functional information could improve risk stratification.

Two studies found that the combination of ultrasound and serum biomarkers (such as FGF-23) improved the prediction of cardiovascular events compared to each method alone.

Usefulness in risk stratification

Twelve studies evaluated the added value of ultrasound calcification detection in cardiovascular risk stratification:

- The presence of calcifications improved risk reclassification (NRI 0,15-0,32) over traditional risk factors in patients with CKD.^(27,28) This was especially useful in patients initially classified as intermediate risk.
- Serial assessment of calcification progression allowed the identification of high-risk patients who

benefited from more intensive therapies.^(29,30) The progression rate was a stronger predictor than the baseline presence of calcifications.

- The absence of calcifications identified low-risk patients, avoiding overtreatment.^(31,32) This could be useful for individualizing the intensity of monitoring and treatment.

Three studies found that incorporating ultrasound calcification assessment into specific CKD risk algorithms significantly improved their predictive performance.

Therapeutic implications

Seven studies explored therapeutic implications of calcification detection:

- The presence of calcifications guided the use of non-calcium phosphate binders in dialysis patients.^(33,34) This was associated with slower progression of calcifications and better cardiovascular outcomes.
- The progression of calcifications was associated with a poorer response to statins, suggesting the need for additional therapies.^(35,36) This could help identify patients who require more aggressive lipid management strategies.
- Calcification regression was associated with a better prognosis in patients who received a kidney transplant.⁽³⁷⁾ This suggests that calcifications could be a reversible therapeutic target.

Two pilot studies explored the use of therapies aimed at inhibiting vascular calcification (such as vitamin K analogues), using ultrasound as a marker of treatment response.

DISCUSSION

The evidence reviewed suggests that ultrasound's detection and assessment of vascular calcifications has significant relevance in managing patients with chronic kidney disease (CKD). The studies analyzed indicate that vascular calcifications are highly prevalent in this population and are associated with increased cardiovascular risk and mortality.

Ultrasound is emerging as a valuable tool for detecting vascular calcifications due to its noninvasive nature, low cost, and ability to perform repeated assessments. Compared to other imaging techniques, such as computed tomography or plain radiography, ultrasound offers advantages regarding patient safety and accessibility, especially in resource-limited settings.

The results suggest that ultrasound assessment of calcifications in the abdominal aorta and femoral arteries provides relevant prognostic information. The presence of aortic calcifications was associated with an increased risk of cardiovascular mortality (HR 1,8-3,2) in patients with advanced CKD and on hemodialysis, while iliac/femoral calcifications were associated with an increased risk of cardiovascular events (RR 1,6-2,4) in patients with stage 3-5 CKD. These findings are consistent with previous studies demonstrating the importance of vascular calcifications as a cardiovascular risk factor in CKD.

Early detection of these calcifications could allow for more timely interventions to mitigate cardiovascular risk in patients with CKD. Furthermore, incorporating ultrasound calcification assessment into CKD-specific risk algorithms significantly improved their predictive performance, suggesting its potential utility in cardiovascular risk stratification in this population.

Despite the promising findings, it is important to recognize several limitations in the reviewed evidence: 1) Heterogeneity in assessment methods: Studies used different protocols and criteria for ultrasound assessment of calcifications, making direct comparison of results difficult. 2) Sample size: Some studies included relatively small samples, which may limit the generalizability of the findings. 3) Long-term follow-up: Few studies provided long-term follow-up data to assess the impact of interventions based on calcification detection. 4) Inter-observer variability: The interpretation of ultrasound images may vary between observers, highlighting the need for standardized protocols.

The review process also had limitations: 1) Publication bias: Studies with negative or non-significant results may not have been published, which could bias the conclusions. 2) Language restriction: The review was limited to articles in English and Spanish, which may have excluded relevant evidence in other languages. 3) Variability in methodological quality: The quality of the included studies was variable, which could affect the strength of the conclusions.

Clinical practice:

- Ultrasound should be considered a first-line tool for assessing vascular calcifications in patients with CKD.
- Standardized protocols for the ultrasound assessment of vascular calcifications in nephrology practice are recommended.

Health policies:

- The inclusion of echocardiographic assessment of vascular calcifications should be considered in CKD management guidelines.
- Training for healthcare professionals in performing and interpreting these echocardiographic assessments should be promoted.

Future research:

- Large-scale prospective studies are needed to validate the prognostic value of calcifications detected by echocardiography at different stages of CKD.
- The efficacy of early interventions based on ultrasound detection of calcifications to reduce cardiovascular risk should be investigated.
- Ultrasound scoring systems should be developed and validated to quantify vascular calcification burden in a standardized manner.

CONCLUSIONS

The detection and assessment of vascular calcifications using ultrasound is emerging as a valuable tool in the management of patients with chronic kidney disease (CKD). It offers a noninvasive, accessible, and low-cost alternative to other imaging techniques. The evidence reviewed suggests a high prevalence of vascular calcifications in patients with CKD, associated with a significant increase in cardiovascular risk and mortality in this population.

Early detection of vascular calcifications by ultrasound has the potential to facilitate timely interventions to mitigate cardiovascular risk in patients with CKD. However, further studies are needed to validate the long-term clinical impact of this strategy.

Further research, particularly large-scale prospective studies, is needed to establish the prognostic value of calcifications detected by ultrasound at different stages of CKD and evaluate the efficacy of early interventions based on these findings.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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