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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

experimental vascular calcification and point to the possibility of being able to modify its *clinical* progression, including dialysis patients.[7,23–26] Nevertheless, it should be recognised that there is no definitive proof in any randomised clinical study showing that a single drug in this therapeutic area has an irrefutable impact on major events in CKD patients.[8,9]

Recent information about phosphate binders

Hyperphosphataemia is recognised as an independent CV risk factor. Abnormal P metabolism occurs early in CKD and there is a general consensus that it is one of the most important factors contributing in the onset of CV calcification, along with changes in intra- and extracellular Ca content. Both have a strong influence on the vascular smooth muscle cell (VSMC) function.[27,28] Since the experiments by Jono et al.[27] and Giachelli et al.,[29] nephrologists have recognised the need to avoid P overload, not only as a promoter of secondary hyperparathyroidism, but also because of its direct effects on CV health,[30–32] including its potent proinflammatory and oxidative effects[33,34] that may affect even patients with mild CKD and possibly the general population.[35]

Goodman et al.'s initial publication in adolescents on dialysis, showed that they already had vascular calcifications and that the amount of Ca they ingested was double than those without calcifications. This information started a broad debate about the different binders (calcium vs. non-calcium) that has not been fully resolved yet.[36–38] Several randomised studies conducted in adults on dialysis have demonstrated that CV calcification progression was truly modifiable by choosing non-calcium P binders.[7,39–42] However these results are not consistent.[43] In some clinical trials, negative results have been attributed to a patient population that had a higher number of CV risk factors;[44,45] other studies faced obstacles such as a small sample size or the use of high Ca concentrations in the dialysate bath in many patients.[46] Therefore, despite the fact that the "Dialysis Clinical Outcomes Revisited" (DCOR) study found that using sevelamer HCl in dialysis patients did not significantly improve the mortality rates,[47,48] the 2009 KDIGO guidelines proposed a restriction of Ca-based P-binder dose in the presence of arterial calcification (guideline 4.1.5; 2C), at least until more conclusive studies are conducted.[30] This represents a step forward in comparison to the previous American guidelines[49] (K-DOQI 2003) where, curiously, the Ca-based P binders were limited only to cases with *severe* vascular calcification (a situation that may be too advanced to modify the harmful consequences). Although the DCOR study did not strictly demonstrate the superiority of sevelamer versus calcium-based binders, it cannot be said that Ca-based P binders are safe.[32,50] With need to take into consideration also economic aspects,[51] at least these studies have made the nephrology community aware that indiscriminately using calcium-based binders may be inappropriate and that it might be safer to limit Ca intake to less than 1 g/day in CKD patients.[52] A recent metabolic study demonstrated that even in stage 3b-4 CKD patients ($n = 8$; mean GFR 36 ml/min/1.73 m^2; mean P = 3.8 mg/dl) administering 1.5 g of calcium carbonate converted a neutral Ca balance into a largely positive balance,[53] although it is unknown whether this altered balance is temporal, by inducing adaptation phenomena, or whether this excess of Ca ends up being deposited in extraosseous tissues.

More recent studies in dialysis patients have shown that the progression of vascular calcification was attenuated not only by sevelamer but also bylanthanum and, in two small pilot studies, by the use of P binders containing magnesium.[54–59] A recent meta-analysis has also reinforced the idea that it may be possible to attenuate the progression of vascular calcification with non-calcium P binders.[60] Moreover, in another randomised, open-label, parallel groups study including 466 Italian patients who were starting haemodialysis, sevelamer improved *survival* as compared with calcium-based P binders,[61] although it could not be established a direct relationship between the Ca load and worse outcomes.[61] Furthermore, in another recent meta-analysis, non-calcium P binders were associated with a criticised reduction of overall mortality risk (22%) in CKD patients (mostly dialysis patients treated with sevelamer),[4] in contrast to the negative results from other previous meta-analyses.[37,62] Nonetheless, in some of these studies high doses of binders were administered to achieve protocol objectives; therefore, these results should be extrapolated with caution to those situations in which moderate doses of Ca-based binders are used or those cases in which both types of binders (with and without Ca) are being administered.[63,64] Another study found that normal individuals and patients with stage 3b-4 CKD had a slightly negative or neutral Ca balance while eating a 800 mg/day Ca diet, however with a 2000 mg/day diet, the normal individuals had a slightly positive balance and the CKD patients had a clearly positive balance, at least during the 9 days of the study.[65]

Lastly, a randomised, multi-centre, open-label pilot study conducted in 212 outpatients with stage 3–4 CKD recruited over a maximum of 36 months demonstrated that treatment with sevelamer to maintain plasma P within the normal range, was associated with a significantly lower incidence of de novo CAC among patients with no baseline CV disease (12.8% vs. 81.8% for sevelamer and Ca carbonate, respectively), as well as slower CAC progression among the patients with evidence of CAC at the start of the study.[66] A significant *regression* of CAC was also detected in 24 patients treated with sevelamer, and only in 2 patients treated with Ca. The overall mortality and the final composite endpoint of death and dialysis inception were lower in the patients assigned to sevelamer.[66] This study did not include a placebo arm and included patients with moderate hyperphosphataemia (4.84 ± 1.3 mg/dl). Conversely, in another, smaller randomised study of 148 patients with moderate CKD (GFR = 20–45 ml/min/1.73 m^2 with a mean P of 4.2 mg/dl) comparison of Ca phosphate binders, sevelamer, and lanthanum vs. placebo showed a completely unexpected increase in vascular calcification in all groups, even though in the post hoc analysis, the degree of progression was higher in the Ca arm.[67] In another study,[68] rosuvastatin and sevelamer did not delay the progression of vascular calcification in CKD patients not yet in dialysis. Therefore, despite the demonstrated potential benefit for survival, at least in some CKD patients, additional studies are needed to define the effects of P binders in CKD patients before starting dialysis. In fact, this is one of the areas of nephrology in which we have less

evidence and limited alternatives. A large controversy has been generated on whether P binders should be prescribed in stage 3–4 CKD,[69–71] this controversy illustrate the extreme necessity to conduct prospective clinical studies measuring hard events.[69–71] According to the prescribing information, P binders without Ca should be restricted to CKD patients not in dialysis if serum P is greater than 1.78 mmol/l (5.5 mg/dl). Nevertheless, it should be noted that in the recent controversies on the KDIGO guidelines,[63] the concern about Ca overload as a risk factor for progression of vascular calcification in CKD was clearly emphasised.[37,66,67,72,73]

Controlling secondary hyperparathyroidism with calcimimetics

In addition to the experimental data showing a neutral or protective effect of calcimimetics on uraemic *atherosclerosis* or vascular calcification,[24,74,75] a randomised clinical trial recently demonstrated that cinacalcet, along with low-doses of vitamin D analogues, can attenuate the progression of vascular calcification in dialysis patients versus the standard treatment (different doses of vitamin D analogues or binders).[25] Although the study did not clearly demonstrate a significant benefit ($p = 0.07$), there was a clear tendency towards decreased progression of CAC, thoracic aorta calcification, and cardiac valve calcification in the group treated with calcimimetics. This effect was especially significant in those patients adhering to the initially designed protocol maintaining a low dose of vitamin D analogues.[26] Similar results were described in an observational study conducted in Japan.[76] Furthermore, another retrospective study including dialysis patients on intravenous vitamin D therapy (a surrogate marker for secondary hyperparathyroidism), the prescription of calcimimetics was associated with a significant improvement in survival.[77] However, the EVOLVE study,[78] comparing calcimimetics vs. standard therapy in the largest study conducted in haemodialysis patients (3883), showed that cinacalcet did *not* significantly reduce the risk of death or CV events in dialysis patients with moderate to severe secondary hyperparathyroidism after an *unadjusted* intention-to-treat statistical analysis. Similarly, in a recent meta-analysis, based essentially on the above study, calcimimetics did not seem to improve CV or overall mortality.[79] As a result, as previously observed with sevelamer in the DCOR study,[47,48] it was not possible to definitively establish a direct relation between therapeutic measures that potentially attenuate vascular calcification progression in dialysis patients and benefits for survival. However, it is important to note that, in addition to other *nominally* significant beneficial effects associated with sevelamer and cinacalcet,[47,48,78] it was observed in both studies that age had a highly significant interaction on the treatment effect. Both drugs significantly reduced mortality in a *predefined* subgroup of patients over 65 years of age; this result is likely due to the higher statistical power inherent to a higher number of CV events and mortality in this age group.[78,80] A similar interaction with age was observed with lanthanum carbonate.[81] In addition, in the general population a significant association between vascular calcification and kidney function has also been recently described in the elderly, but not in younger individuals.[82]

It is important to note that, in the case of the EVOLVE study, cinacalcet *did* significantly reduce the risk of death or major CV events in dialysis patients in a second predefined intention-to-treat analysis when *adjusted* for age or other factors, as well as other complex sensitivity analyses, despite the excessive number of *drop-ins* and *drop-outs*.[78,83] Various beneficial effects of cinacalcet have also been described in post hoc studies,[83–88] including decreased mortality in non-atherosclerotic events (including sudden death and heart failure) in patients treated with cinacalcet.[86] We therefore believe that the EVOLVE study should not be considered a *negative* study, but rather an inconclusive, non-definitive study, since the absence of evidence cannot in any way be considered evidence of absence.[50,83]

Lastly, it is important to emphasise that calcimimetics have also been successfully used to treat some cases of calciphylaxis.[87,89] Calciphylaxis episodes occurred significantly less often in the group of patients treated with cinacalcet in the EVOLVE study and in a post hoc analysis.[78,87]

Calcidiol and vitamin D receptor activators

Low levels of calcidiol (25-OH vitamin D) have been directly associated with the presence and progression of vascular calcification and represent a new CV risk marker on their own.[90,91] Although it may only be a mere bystander maintaining "normal" levels seems to be desirable. Spanish guidelines[92] recommended to maintain normal levels of calcidiol to reduce vascular calcification progression, maintain a normal bone turnover,[6,91] and provide the other pleiotropic effects described for vitamin D, including vascular regeneration, anti-inflammatory effects, and anti-renin activity, among others.[93–96] However, there are no *prospective*, randomised clinical trials that have assessed the impact of *native* vitamin D or vitamin D receptor (VDR) activators such as calcitriol, alfacalcidol, paricalcitol, or others on human vascular calcification. Experimental studies have demonstrated differential effects between calcitriol and other VDR activators on extraosseous calcification. Calcitriol is a classic, direct, dose-dependent inducer of *experimental* vascular calcification, especially in the presence of high P exposure or as the result of systemic vitamin D-induced Ca and P accumulation, more than a local effect on the artery wall.[24,74,97] Furthermore, the lowest doses of both calcitriol and paricalcitol seem to protect against vascular calcification, likely through klotho restoration and osteopontin expression.[98–100] Therefore, the presence of a bimodal effect of the VDR activators regarding vascular calcification regulation can be postulated. In general, experimental data supporting lower toxicity with some VDR activators versus calcitriol are not consistent between studies, but they seem to support the assertion that there is reduced calcification induction with other selective VDR activators such as paricalcitol.[24,74,95,101] For example, paricalcitol, in contrast to calcitriol, decreases Wnt/β-catenin pathway activation, the most important signalling pathway in transdifferentiating VSMC into osteoblasts.[102] Paricalcitol may also have an effect on earlier stages of vascular disease; it is unknown whether this is true of other VDR activators.[103] Furthermore, several *retrospective* studies have

described a consistent and solid benefit on survival for haemodialysis patients with *selective* VDR activators[104,105] and, although it has been questioned,[106] the benefit seems to be more pronounced in the low-dose range and among patients who received selective VDR activators.[18,104] Lastly, a recent meta-analysis including 14 observational studies (194,932 patients) showed that VDR activator therapies are associated with a lower mortality in CKD patients,[107] although there is no consistency between the different meta-analyses.[108] To date there is no published prospective clinical trial assessing the effect of VDR activators on survival so the previous potential beneficial results could be confirmed, although by no means this beneficial effect should be rejected either.[109]

Vitamin K

Vitamin K is necessary as a cofactor in the process of converting inactive decarboxylated extracellular matrix proteins into active carboxylated proteins. Osteocalcin and Matrix Gla protein (MGP) require the presence of vitamin K for activation and warfarin, as a vitamin K antagonist, inhibits coagulation, but long-term use can promote vascular calcification and overregulation of decarboxylated MGP.[110,111] The association between CAC and vitamin K antagonist therapy was already known in patients with low-risk atrial fibrillation[112] and, recently, Górriz et al. confirmed the independent association between the use of oral anticoagulants and vascular calcification, even in CKD patients not on dialysis.[113] Experimental work shows that vitamin K is able to revert warfarin-induced medial calcinosis of elastin[114] and, since vitamin K deficiency is common in dialysis, it is not surprising to see that currently there are several prospective clinical trials evaluating the effect of vitamin K supplementation on CAC progression in CKD and haemodialysis patients.[115] It is possible that the new oral anticoagulants, now available for patients with atrial fibrillation or acute coronary syndrome, may become a therapeutic alternative.[116,117]

Preliminary data on bisphosphonates, thiosulfate, and phytates

Bisphosphonates have also been successfully used "off label" to treat calciphylaxis.[118] In addition to the experimental data showing that treatment with pamidronate or etidronate prevents vascular calcification,[119] oral or parenteral etidronate can delay CAC progression and aortic valve calcification, although not all new-generation of bisphosphonates have been shown to reduce calcifications.[120–123] In this line, it is worth to mention that the vessel wall possesses a "natural form of bisphosphonates", pyrophosphates, which antagonise alkaline phosphatase and are one of the most effective anticalcifying factors of the vascular wall.

A randomised clinical trial including 108 hypercholesterolaemic patients revealed that combination therapy with atorvastatin plus etidronate for 12 months significantly reduced atheroma plaques in thoracic and abdominal aorta.[124] Since the vascular effects of bisphosphonates cannot be separated from adequate bone formation, the administration to CKD patients may promote the development or aggravation of adynamic bone disease.[30,125,126] As a result, a bone biopsy is recommended before using bisphosphonates in patients with a GFR < 30 ml/min/1.73 m^2 unless a *high*-turnover bone disease is undeniably present,[30] or in the context of a potentially fatal disease such as calciphylaxis.[118] A similar strategy should likely be applied to new therapies such as denosumab and romosozumab, although the half-life of these drugs in bone is certainly lower.[127]

Sodium thiosulfate has been introduced into the therapeutic arsenal against calciphylaxis.[128] It may also attenuate the CAC progression rate versus the non-treatment group, but with a significant decrease in hip bone mineral density.[129,130] Sodium thiosulfate and other binding agents have been demonstrated to be potentially useful in reversing vessel medial calcification,[131] however the mechanism by which sodium thiosulfate reduces calcification is not fully understood.[129,132]

Given the importance of this topic, new drugs are being developed that could act as vascular calcification inhibitors such as *SNF472*,[133] an intravenous formulation of myoinositol hexaphosphate (phytate) that prevents hydroxyapatite crystals from forming and growing.[134,135] It also acts as a calcification antagonist that could be effective as a therapy for treating CV calcification in CKD patients and in calciphylaxis.[133] SNF472 acts through a physicochemical mechanism, binding to the forming or growing crystal.[136] Its high efficacy in animal models and short half-life give it a suitable safety and efficacy profile in CKD, but this will have to be confirmed in long-term clinical studies. At this time it is in phase 1b/2 development.[136]

Other possible treatments

There are no studies investigating the effects of *parathyroidectomy* on the progression or regression of vascular calcification that meet the pre-established inclusion criteria for the 2009 KDIGO guidelines revision. Similarly, to date there are no new data available beyond the classic indication for parathyroidectomy in the form of calciphylaxis associated with severe secondary hyperparathyroidism. In *kidney transplantation*, few studies have been able to demonstrate stabilisation or attenuation, but do not completely stop, the rate of progression of vascular calcification, despite the significant improvement in kidney function and mineral metabolism parameters.[137–140] However, many other CV risk factors, either prior to or within the context of transplantation, may play an additional role in this specific population.

General recommendations

There are no studies demonstrating that the presence/absence/degree of vascular calcification is associated with changes in the prognosis of CKD patients; however, in this second part of the review we have discussed the extensive evidence, especially in dialysis patients, that some of the treatments used for CKD–MBD may enhance vascular

calcification progression, at least when the calcifications are already present.[7,25] It is known that vascular calcification is a late, and likely secondary, phenomenon, preceded by inflammation, among other factors, that could be primarily treated by preventing CV disease at earlier stages.[4] However, given the lack of proven strategies for early prevention, along with the serious possibility of inducing iatrogenic effects, makes us believe that a nihilistic attitude towards vascular calcification is not appropriate, considering it as an impossibility to treat, since it has been demonstrated that we can both attenuate its progression or even turn it worse.[5,7–9,25,50]

Awaiting the difficult viability of a randomised, multi-interventionist clinical trial independent from drug industry, we recognise that CV calcification does not meet the requirements to recommend general screening.[141,142] However, given the predictive capability of CV calcification and its *progression*, we believe that CKD patients with vascular calcification would not only require more continuous CV follow-up and monitoring (not only for their calcification), but would likely benefit from additional initiatives to control the traditional and non-traditional CV risk factors.[6,143] Among these initiatives we should include more intensive control of plasma P, avoid P overload, administration of fewer treatments or high doses of drugs that could promote CV calcification, which may result in increasing the value of certain treatments above their absolute cost.[7,37,78,83,95,144] The recent arrival of some generics will undoubtedly help to reduce certain economic burdens while waiting for new evidence.[8,9] Knowing the presence/absence/degree of CV calcification would improve the individual CV risk assessment, and would help to choose the safest treatment option to avoid the risk of increasing the burden and progression of CV calcification; always considering the high risk of CKD patients and the indirect economic consequences.[6] CV calcification should be assessed in all patients or only in selected cases depending on the resources available in each country.[6] Obviously, the arrival of much less expensive generic drugs could make it easier to use drugs with a better therapeutic margin without the need of strict prescreening.

Different studies have shown consistently that once vascular calcification is established it follows a progressive, and likely accelerated, course.[145] Therefore from a purely academic perspective, it is clear that the use of non-Ca-based P binders should be encouraged, especially in patients who already have vascular calcifications and in those with low levels of PTH or alkaline phosphatase. Patients with specific characteristics may also benefit from non-Ca-based P binders, e.g. over 65 years with a reasonable life expectancy,[47,81] diabetics, treated with warfarin, incident dialysis patients in whom it is anticipated a long time on the transplant waiting list, young CKD patients in whom a long evolution is expected, or patients with proven progression of vascular calcification. Magnesium and iron deficiency should probably be avoided as well, especially in these patients.

Some patients with moderate–severe secondary hyperparathyroidism should be preferentially treated with calcimimetics or low-dose VDR activators.[25,78] *Native* vitamin D or selective VDR activators could be preferentially considered in patients with vascular calcification with low serum calcium without hyperphosphataemia, and native vitamin D in patients with suspected adynamic bone disease[92,146]; in addition, exposure to high Ca concentrations in the dialysate bath should be limited,[125,147–149] including peritoneal dialysis patients.[150] In any case, the KDIGO guidelines propose an assessment of vascular calcification in *any* patient in whom awareness of its presence could influence therapeutic decision.

As we have shown in the first part of this review, we consider that initial assessment of vascular calcification should be done with unsophisticated plain X-rays, and we believe that the presence of vascular calcification, especially in muscular arteries such as hands arteries, would emphasise the need to control Ca–P metabolism-related factors (and each nephrology community would need to establish an Adragao score interval where the most expensive treatments should be implemented depending on the different finantial resources).

Finally, it is known that patients who do *not* present valve or vascular calcification have a good prognosis during the following years and it is likely that the future of these patients will not be in danger if more economical medications are used, should that priority be above academic considerations. Nevertheless, it is obvious that studies aimed to confirm these ideas, as well as the recommendations related to the imaging technique used and re-analysis periodicity, especially in young patients who are not candidates for kidney transplant within a reasonable period of time.

Conclusions

CKD patients present a very high risk of CV disease and premature death; therefore we should offer them the opportunity to have the best prevention and treatment possible. Unfortunately, though the absolute costs are a concern, quantitative or qualitative knowledge of CV calcification could help to optimise economic resources and to assign the more expensive treatments to the patients with greater expectations of improvement. Therefore, we believe that CV calcification should be part of future protocols and clinical studies since it is a distinguishing characteristic of CKD–MBD, it is a valid predictor of clinical evolution, it is modifiable, and its progression seems to increase with certain treatments (iatrogenic effect) whereas others strategies seem to attenuate it. Obviously, assessing vascular calcification only makes sense if the result can be used by the nephrologist to make treatment decisions, especially early decisions, especially early in the course of the disease, and with the possibility of following the Hippocratic principle of “first, do no harm” or the more recent “prevention is better than cure”.

Key concepts

- CV calcification is part of CKD–MBD.
- The 2009 KDIGO guidelines (and the 2015 publication of their preliminary controversies) and the 2011 Spanish guidelines deem it reasonable to use information on vascular calcification to guide CKD–MBD management.
- Assessment of CV calcification should be performed in all patients, or only in selected cases depending on the

resources available in each health care system. This is as long as the information on the absence/presence/degree of vascular calcification may affect treatment decisions.

- CV calcification is a potentially modifiable risk factor.
- CV calcification progression increases with certain treatments (potential iatrogenic effects) whereas other drugs seem to attenuate it.
- In *clinical* studies and meta-analyses, non-calcium-based phosphate binders or calcimimetics seem to attenuate clinical progression of vascular calcification versus calcium-based P binders or standard treatment regimens for secondary hyperparathyroidism without calcimimetics.
- *Experimental* models demonstrate that different vitamin D compounds (calcitriol vs. *selective* vitamin D receptor activators; e.g. paricalcitol) have differential effects on vascular calcification.
- There is preliminary data on the influence of other drugs (e.g. vitamin K, bisphosphonates, sodium thiosulfate, or SNF472) on vascular calcification progression in CKD patients.
- Although there is no definitive proof that personalised treatment based on the presence/absence/degree of vascular calcification improves survival of CKD patients, a nihilistic attitude does not seem justified.

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