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CKJ Review

CKJ REVIEW

Can we reverse arterial stiffness by intervening on CKD-MBD biomarkers?

Marc G. Vervloet

Amsterdam University Medical Centres, Nephrology, Amsterdam, The Netherlands

Correspondence to: Marc G. Vervloet; E-mail: m.vervloet@amsterdamumc.nl

ABSTRACT

The increased cardiovascular risk of chronic kidney disease may in part be the consequence of arterial stiffness, a typical feature of kidney failure. Deranged homeostasis of minerals and hormones involved (CKD-MBD), are also strongly associated with this increased risk. It is well established that CKD-MBD is a main driver of vascular calcification, which in turn worsens arterial stiffness. However, there are other contributors to arterial stiffness in CKD than calcification. An overlooked possibility is that CKD-MBD may have detrimental effects on this potentially better modifiable component of arterial stiffness. In this review, the individual contributions of short-term changes in calcium, phosphate, PTH, vitamin D, magnesium, and FGF23 to arterial stiffness, in most studies assessed as pulse wave velocity, is summarized. Indeed, there is evidence from both observational studies and interventional trials that higher calcium concentrations can worsen arterial stiffness. This, however, has not been shown for phosphate, and it seems unlikely that, apart from being a contributor to vascular calcification and having effects on the microcirculation, phosphate has no acute effect on large artery stiffness. Several interventional studies, both by infusing PTH and by abrupt lowering PTH by calcimimetics or surgery, virtually ruled out direct effects on large artery stiffness. A well-designed trial using both active and nutritional vitamin D as intervention found a beneficial effect for the latter. Unfortunately, the study had a baseline imbalance and other studies did not support its finding. Both magnesium and FGF23 do not seem do modify central arterial stiffness.

LAY SUMMARY

Abnormalities in mineral metabolism as it occurs in chronic kidney disease, are independent contributors to cardiovascular complication for these people. Here, it is reviewed whether these abnormal levels of minerals have an impact on stiffening of arteries. This pathological feature has been shown previously to have a detrimental impact on both the heart and perfusion of organs. It was found that calcium and possibly the parathyroid hormone may indeed promote arterial stiffness. This knowledge may influence treatment choices.

Keywords: arterial stiffness, augmentation index, calcification, cardiovascular, CKD, CKD-MBD, dialysis

INTRODUCTION

It is well established that chronic kidney disease (CKD), defined as a chronic estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, is an independent risk factor for mortality and cardiovascular disease [1]. Since such a decline in GFR generally is irreversible (unless kidney transplantation is performed), many observational studies have searched for components of CKD that carry this risk and might be targetable, with the aim to mitigate a part of this risk. A conundrum

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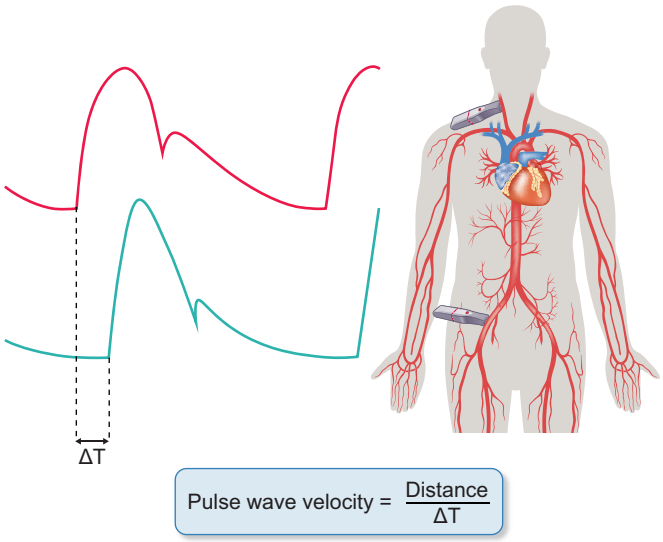

Figure 1: Carotid-femoral pulse wave velocity (cfPWV) is measured by the simultaneous determination of the pulse wave at the carotid and femoral artery. The time difference between the initiating upslope of the pulse wave is established. In addition, the difference in distance travelled at the two anatomical location is measured form the sternal notch as reference point. The velocity is then calculated as distance/time (permission from thoracickey.com).

in nephrology is that while several CKD-specific risk factors, in particular those related to chronic kidney disease-mineral and bone disorders (CKD-MBD), have been identified and can be modified, interventions on CKD-MBD have not led to improved cardiovascular or mortality outcome. In turn, outside the spectrum of CKD-MBD, reducing proteinuria and correcting metabolic acidosis most likely does retard progression of CKD [2, 3]. Sodium glucose transporter 2 inhibitor (SGLT2i) treatments have recently been established as a cornerstone of risk reducing interventions in people with CKD, although its mechanism of protection has not been fully elucidated [4, 5]. Of note, SGLT2i also provides protection in patient populations without overt kidney disease [6], which argues against an exclusive CKD-specific underlying pathophysiological process. The discovery of the virtually generic protective effect of SGLT2i was unexpected, because it was not based on pre-existing knowledge of an identified underlying mechanism that carries CKD-specific risk. Apart from these interventions, targeting calcium balance, vitamin D deficiency, abnormal phosphate homeostasis including early increments of FGF23, and secondary hyperparathyroidism, even though highly prevalent in (advanced) CKD, have not been shown to lower cardiovascular risk. This contrasts with several treatments that address CKD-nonspecific risk factors such as hypertension and diabetes [7–9], which have been shown to be of benefit in terms of clinical outcomes including the progression of CKD.

The question therefore arises as to how to explain the discrepancy between observational data that suggest a causal role for biomarkers of CKD-MBD on clinical outcome, and the absence of trial data that support a causal role for these factors. One explanation is that residual confounding of observational studies exists and other, so far unidentified factors, explain these associations. In turn, clinical trials may have missed their primary outcome (type II error), because of recruiting low-risk participants only, too-small sample sizes, too-short study duration, or a too-small effect size on the CKD-MBD component that were modified by the intervention. Another explanation can be that the effects of disturbed mineral homeostasis are not direct, but are mediated by the changes they may induce in functional or structural properties of the cardiovascular system. If the relation between a CKD-MBD biomarker and such an intermediating phenomenon is not linear, then the toxicity of the biomarker depends on its effect on that intermediating phenomenon. An example of the latter is the finding that, in healthy people, a diet high in phosphate induced an increase in arterial blood pressure, and this effect appeared to be driven by activation of the sympathicoadrenergic axis [10]. In this setting, one can conclude that a part of the association between phosphate intake and cardiovascular outcome is present only if increases of blood pressure or sympaticoadrenergic activity occur. Clearly, observational studies generally adjusted for blood pressure, but disturbances in mineral metabolism may affect other factors as well that can influence cardiovascular risk, but are not generally measured or reliably quantifiable. Among these potentially intermediating factors are the presence, amount and progression of vascular calcification (VC), the evolution of left ventricular hypertrophy, and arterial functional characteristics such as endothelial dependent vasodilating capacity and arterial stiffness. In this narrative review, the focus is on the influence of calcium and vitamin D, phosphate, and PTH on arterial stiffness, usually measured as pulse wave velocity (PWV).

Arterial stiffness

Vascular stiffness can be defined by the ratio of intraluminal pressure and vessel diameter. Measuring arterial stiffness would then require the simultaneous measurement of intraluminal pressure and vessel diameter on the same location. That is both impractical and reflects stiffness in that location only. Therefore, most studies make use of the fact that the velocity of transduction of a pressure pulse along the vessel is dependent on the stiffness of that vessel, with higher velocities for stiffer vessels. The time interval between the arrival of a pressure pulse, generated by the contraction of the left ventricle, on two different locations of the arterial tree is therefore a function of arterial stiffness. If the distance between these two locations is known, the PWV dan be determined (meters per second, m/s), as shown in Fig. 1. It is important to realize that PWV is a distinct entity

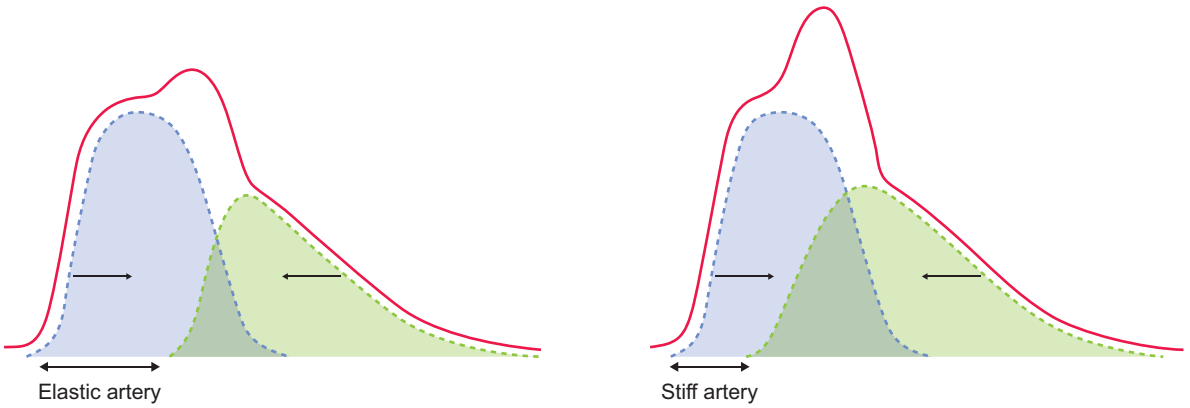

Figure 2: Central pulse wave for an normal elastic arterial system (left) and for a stiffened arterial system (right). The cumulative pressure, indicated in red, is the sum of the antegrade pressure wave (blue wave) and the distally reflected retrograde pressure wave (green). In elastic central arteries the reflelcted wave arrives back centrally rather late, largely during diastole and provides energy for coronary perfusion. With stiffened arteries, the higher pulse wave velocity leads to an earlier return of the reflected wave augmenting systolic pressure, and providing less energy during diastole for coronary perfusion (reproduced with permission).

from blood flow, and independent from it. In clinical research practice, the two sites are selected where the arterial pulses can be palpated, and therefore brachial-ankle (ba) or carotid-femoral (cf)PWV, or PWV of other segments can be measured [11]. Some devices deduce arterial stiffness from pulse wave analysis, but these are generally considered less accurate [12].

- Arterial stiffness is consistently associated with cardiovascular disease.
- The best validated method to assess arterial stiffness is PWV.
- CKD itself increases arterial stiffness.
- In kidney disease, arterial stiffness is the consequence of arterial calcification, other structural abnormalities in the vessel wall, and functional properties.

Arterial stiffness has two detrimental effects, one upstream from the studied segment, usually the aorta, and one downstream. The upstream effect is the earlier retrograde return of reflected pressure pulse in the ascending aorta as a consequence of an increase in PWV. This augments the central systolic blood pressure and hence workload for the left ventricle, and decreases central diastolic blood pressure, which impairs coronary perfusion (Fig. 2). The downstream effect is that loss of compliance of the aorta exposes highly perfused organs, in particular the brain and kidneys, to higher pulse pressure and more pulsatile flow. In line with this, a recent meta-analysis demonstrated that cfPWV is an accurate and independent predictor of all cause, and in particular cardiovascular, mortality in non-CKD populations [13, 14]. This predictive value of arterial stiffness also applies to patients with CKD [15] and end stage kidney disease (ESKD) [16, 17]. In addition, besides being a predictor of these endpoints, in patients with CKD a higher PWV also is associated with steeper declining eGFR slope and more early commencement of dialysis [18]. Of note, CKD itself appears to worsen arterial stiffness. It is obvious that arterial wall calcification is a major determinant of PWV. Indeed, a study that determined the presence of arterial wall calcification found a strong association of PWV with especially abdominal aorta calcification [19]. Discussing the role VC is outside the scope of this overview, because it is generally considered not to be modifiable and has been reviewed previously [20]. Apart from calcification, other structural and functional properties of the arterial wall contribute to stiffness as well, such as degradation of elastin fibers, changes in interstitial collagen and other matrix components, and tone of vascular smooth muscle cells. Currently, it is unknown whether improving arterial stiffness directly improves clinical outcome. In addition, it is unlikely that all determinants of arterial stiffness have been identified. Here, the focus is on how components of CKD-MBD may affect arterial stiffness.

Effects of calcium on arterial stiffness

Several lines of evidence point to a role for calcium on arterial stiffness. Cross-sectional epidemiological data among 565 adults from a general population found that a higher serum calcium was independently associated with higher baPWV after adjusting for potential confounders [21]. A similar result was found among older woman in whom calcium was associated with arterial pulse pressure, whereas vitamin D levels and PTH were not [22]. In another longitudinal study, also among people from the general population, it was found that among those >48 years of age, an increase of calcium (within normal range) was independently associated with increased baPWV [23]. Of note, no effect of changes in phosphate was found. However, in a small intervention study among healthy participants, acute oral calcium loading, either as supplement or from dairy sources, despite a substantial suppression of PTH, did not change any parameter of arterial stiffness [24]. It must be noted that in this study the increase in serum calcium was small (0.07 mmol/l for those with increased calcium intake from diet, and 0.1 mmol/l for those taking calcium as supplement). A role for calcium was also suggested in a multiomics analysis among female twins [25]. That study revealed that methylation of the promotor region of calcium and integrin-binding protein-2 gene (*Cib2*-gene) was a determinant of arterial stiffness. The gene product of this gene is involved in intracellular calcium handling.

Higher serum calcium, within the normal range, is associated with higher PWV, both in the general population as well as in people with CKD. In intervention studies in people treated by hemodialysis, lowering dialysaat calcium concentration improves arterial stiffness within hours. Long-term studies in people on dialysis also support a benefit for lower serum calcium, but whether this benefit is driven by retarding VC is unclear. Higher serum calcium, within the normal range, is associated with higher PWV, both in the general population

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Also in people with ESKD, data support a role for calcium on arterial stiffness. In a single-arm prospective intervention trial among 20 patients on hemodialysis, dialysate calcium was changed from 1.75 to 1.5 mmol/l for 6 months [26]. Aortic PWV improved (15.48 ± 4.50 to 12.88 ± 3.45 m/s) as did Aix (23.3 ± 17.5 to 15.2 ± 19.0 m/s). Remarkably, baPWV, reflecting stiffness of more peripheral arteries, was unchanged. The changes observed in aortic stiffness followed changes in serum calcium concentrations in the same direction. These in turn were inversely associated with Fetuin A level, a protein involved in and assumed to have protective effects against calcium and phosphate mineral stress [27]. However, these observations must be interpreted with caution. Being a single-arm study, there was no comparator, so the spontaneous evolution of PWV was not followed. In addition, over time, phosphate and PTH increased and in several participants vitamin D was started during the study period: all changes that may have influenced the observed changes in aortic vascular stiffness. Indeed, in a prospective observational study of 289 patients on hemodialysis, which were followed for 6 months on dialysate calcium of 1.0; 1.25; 1.35 or >1.5, there was an increased PWV in all, with no different change per group [28].

More insightful are results from comparative interventional studies. In a short-term cross-over trial different calcium concentrations (1.0; 1.25 and 1.5 mmol/l) in dialysate were compared. This study found an immediate effect showing increased crPWV and cfPWV after dialysis compared to predialysis for higher calcium in the dialysate. This higher PWV also induced a more pathological central pressure waveform (Fig. 3). This change was paralleled by changes in serum calcium concentrations [29]. Another short-term study compared low calcium dialysate (1.25 mmol/l) with high (1.75 mmol/l) in a cross-over design, and measured stiffness before, during, and immediately after dialysis using digital volume pulse analysis [30]. Arterial stiffness increased during dialysis to 15% above baseline when the high calcium dialysate was used, which, also in this study, paralleled an increase of serum calcium. There were no changes in the lower calcium dialysate group. In another trial, hemodialysis patients treated by regional citrate anticoagulation were titrated to a lower or higher concentration of ionized calcium during a single dialysis session (and the reversed order in another session) after which PWV was determined and compared to PWV prior to that dialysis session [31]. PWV increased with higher calcium levels and decreased with lower calcium concentrations during each session. These changes were independent from changes in blood pressure. These very short-term effects of higher calcium exclude that this was mediated by progression of VC, but for instance increased the tone of vascular smooth muscle cells. However, it cannot be excluded that after longer exposure to higher dialysate calcium, an effect on aortic calcification may play an additional role. The effect of longer exposure to differences in dialysate calcium has been studied as well. Twenty-seven patients were randomized to Ca dialysate 1.12 or 1.37 mmol/l. Aortic stiffness, as measured by cfPWV increased in the high group from 14.6 ± 5.9 at baseline to 17.0 ± 6.7.0 m/s after 6 months, and was unchanged in low Ca group. Interestingly, no changes were observed in carotid-radial PWV, which indicates different effects on the aorta as compared to the brachial artery [32], a finding that was also observed in the short-term study described before.

Data for patients treated with peritoneal dialysis (PD) are sparse. In a prospective observational study among 49 patients, it was found that baPWV increased after 6 months (from 8.4 ± 1.1 to 9.6 ± 2.3 m/s) for those using PD fluids containing 1.75 mmol/l calcium [33]. There was no change in PWV for those using PD fluids that contained 1.25 mmol/l calcium. However, patients were not randomly allocated to either dialysate composition, which undermined the validity of any conclusion.

In summary, there is consistency across studies in showing that higher serum calcium concentration may increase PWV by inducing arterial stiffness.

Vitamin D and arterial stiffness

The vitamin D receptor is present on cardiovascular tissues including cells from arteries [34], and hence it is conceivable it has physiological roles on these structures. Vitamin D deficiency, defined here as a concentration below 50 nmol/l (20 ng/ml) for the general population, is associated with increased risk for mortality, especially cardiovascular mortality, in people treated by hemodialysis [35], in people with CKD [36], and also in the general population [37]. Of note, vitamin D deficiency is also inversely associated with cfPWV in the elderly [38]. This association was only slightly reduced after multivariable adjustments for potential confounders including serum calcium concentration and eGFR. The effects size, however, was small; cfPWV was 8.8 m/s in the lowest tertile, versus 8.6 and 8.5 m/s in the middle and highest vitamin D tertiles, respectively. This may be explained by the fact that most subjects in this study were not vitamin D deplete (mean and SD: 34±12 ng/ml). In a study cohort of people with CKD stages 3–5, with vitamin D levels of 18.15 ± 5.87 ng/ml, lower levels of vitamin D were, with age, the key determinants of baPWV (reflecting peripheral, not central arterial stiffness) [39].

In a non-CKD population with mild vitamin D deficiency at baseline, a monthly dose of 50 000 IU, or a daily dose 4000 IU cholecalciferol for 6–12 months did not improve central PWV [40, 41]. The BEST-D study (Biochemical Efficacy and Safety Trial of vitamin D) was a relatively large trial ($n = >100$ per arm) comparing two doses of vitamin D (2000 and 4000 IU/day) with placebo and found no effect on arterial stiffness, despite doubling plasma levels of 25D [42]. However, overt vitamin D deficiency was not present at baseline, and these negative results may have been the consequence of that. These negative results from this relatively large trial on arterial stiffness are in line with a meta-analysis of several smaller studies [43]. These results contrast to a study among obese African Americans with baseline vitamin D levels of 37±10 nmol/l, in whom monthly doses of cholecalciferol of several dosages were compared in a placebo-controlled study [44]. The highest dose (120.000 IU) reduced central PWV by 10.4% from a baseline value of 6.71 ± 1.41 m/s.

As well as in the general population, the effects of vitamin D supplementation has also been studied in people with CKD. In a double-blind prospective trial, 87 persons with CKD stages 3B and 4 were evaluated after being randomized to either placebo, 0.5 calcitriol thrice week or calcifediol 5000 IU three times a week. Only in the calcifediol group was there a substantial reduction of PWV, while it remained stable in the calcitriol group and increased in the placebo arm [45]. At baseline, however, groups were not balanced: PWV was lower in the placebo group, so it cannot be excluded that regression to the mean explained the apparent benefit of calcifediol.

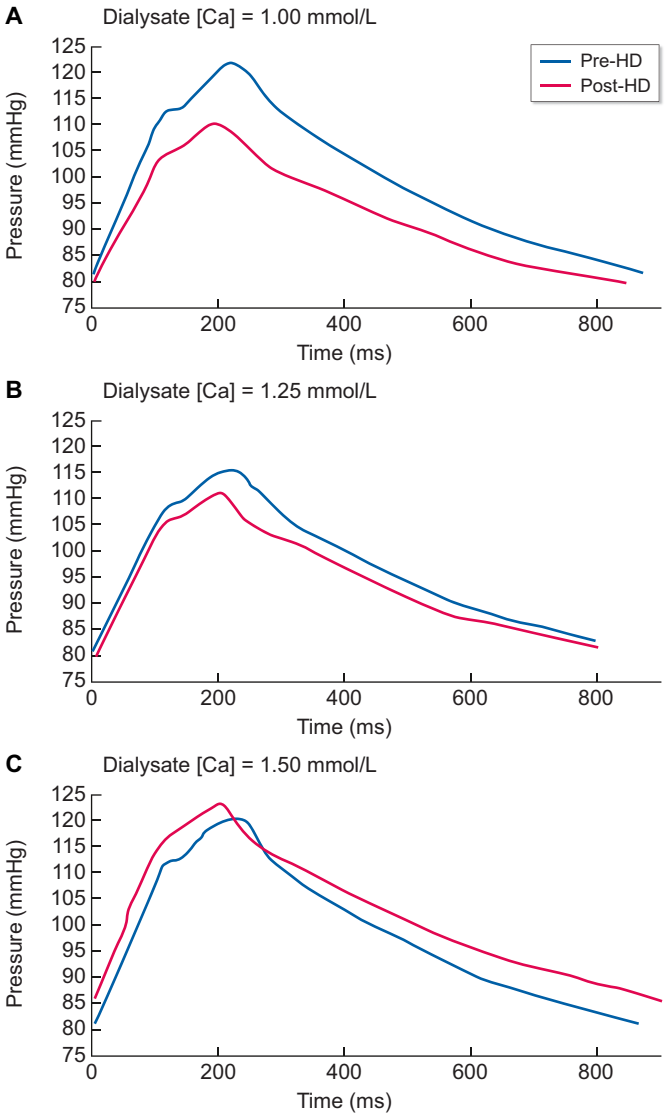

Figure 3: Central pressure curves before (black blue lines) and after (red lines) dialysis, for dialysate calcium of 1.0 mmol/l (top panel); 1.25 mmol/l middle panel; and 1.5 mmol/l (lower panel). The curves show that with increasing dialysate calcium, the post-dialysis pressure curves are increasing compared to predialysis. This indicates increasing arterial stiffness with higher dialysate calcium (modified and reproduced with permission form Lebeouf29).

In addition, most patients had calcifediol levels above 25 ng/ml at baseline, and may be considered not to be vitamin D deficient. In a comparable population in terms of baseline severity of CKD, PWV and vitamin D status, a high dose of cholecalciferol at baseline and after 8 weeks (300 000 IU) had no effect on PWV at week 16 [46]. Limitations of this study were the lack of a comparator and possibly the duration of the study period, which may have been too short to observe treatment effects, despite the fact that vitamin D levels nearly doubled in this period.

A few studies reported on the effects of active vitamin D on arterial stiffness. In a small prospective study among people with stage 3 and 4 CKD, after 1 year of treatment with paricalcitol, an analog of active vitamin D, a small decline in cfPWV 11.8 to 11.2 was observed [47]. In contrast, in another observational study among people treated with hemodialysis, those treated with higher dose of alfacalcidol (>2 μg/week) had a 1.5 m/s increase of cfPWV compared to those using a lower dose after 1 year [48]. However, this study was not randomized, and interpretation of results is hampered by selection bias. More robust are the data from a recent randomized placebo-controlled double-blind trial on 1 year of treatment with oral 0.25 μg calcitriol for 1 year in people with diabetes and CKD, mainly stage 3 [49]. There was no effect of the intervention on the primary outcome, which was aortic PWV.

Collectively, there are no studies using vitamin D, either in its active or nutritional form, that convincingly demonstrate a beneficial effect on arterial stiffness. Although a theoretical benefit of vitamin D may be offset by increments of calcium, which may nullify presumed benefit, the studies described previously that adjusted for calcium still failed to demonstrate a beneficial effect on arterial stiffness by vitamin D.

Effects of phosphate on arterial stiffness

More so than calcium, higher levels of serum phosphate are strongly associated with VC, which in turn is a major determinant of large artery stiffness, as outlined previously. Therefore, studies addressing the effect of long-term exposure to hyperphosphatemia on PWV, will face difficulties in disentangling effects driven by VC and non-VC effects, the latter being the focus of this review.

In MESA (Multi-Ethnic Study of Atherosclerosis), a population with normal to moderately impaired kidney function, serum phosphate concentration was associated with a high ankle-brachial index, a marker of stiffened arteries in the lower extremity [50]. However, larger artery stiffness, as measured by pulse wave analysis after adjustment for age, gender, and race was not associated with serum phosphate concentration. In a cohort of CKD patients (creatinine clearance 51 ± 19 ml/min), augmentation index, an indirect marker of arterial stiffness, was associated with age, systolic blood pressure, gender (higher in females), race (higher in blacks), and inversely with kidney function, but not with serum phosphate concentration [51].

Human experimental data on the effects of phosphate on vascular function are scarce. In two small studies among healthy volunteers, the acute effects of a diet containing high or low phosphate were examined. It was found that flow-mediated dilation (FMD) was impaired by high dietary phosphate exposure [52, 53]. Another study could not replicate these findings, but in that study the intervention did not increase serum phosphate concentration [54]. FMD mainly reflects endothelial cell function of conduit arteries, which may not affect arterial stiffness. This was more explicitly studied in another experiment among healthy volunteers that also measured cfPWV after dietary phosphate exposure. In this study, the intervention induced an increase in serum phosphate concentration 1 and 2 hours after ingestion from 3 to 4.5 mg/dl. This induced a substantial impairment of FMD, but there was no effect on PWV. As well as effects on FMD, there is also evidence that circulating phosphates influence microvascular function [55].

Remarkably, the effects of lowering phosphate concentration form increased toward normal on arterial stiffness has not been studied. However, there are compelling data showing that phosphate binder therapy, in particular, non-calcium containing binders, retard progression of VC [56]. It is reasonable to assume this also has beneficial effects on the evolution of arterial stiffness. However, whether this eventually translates into improved clinical outcome is heavily debated [57, 58].

An 8-week study using sevelamer in normophosphatemic persons with CKD showed improved PWV only in those with less VC at baseline [59]. This effect is unlikely explained by mitigating VC progression because of the short-term follow-up. However, serum phosphate and FGF23 concentration did not change, suggesting that the effects of sevelamer on PWV had a different mechanism. Longer-term studies in normophoshatemic patients with CKD, however, did not detect any effect on arterial stiffness [60, 61]. These trials, however, like the short-term study before, did not accomplish to lower serum phosphate concentration. In a secondary on-treatment analysis of the IMPROVE-CKD trial [61], there was a minor decline of phosphate concentration, but this did not induce any change in PWV.

Reconciling these data on the effect of phosphate on arterial stiffness is complex. While it is likely that chronic exposure to hyperphosphatemia contributes to medial (and possibly also atherosclerotic plaque-) calcification in people with advanced CKD, and thereby contributes to arterial stiffness in CKD, there are no data that support another mechanism or short-term effects of phosphate on arterial stiffness, as is present for calcium.

Parathyroid hormone and its effects on arterial stiffness

One of the hallmarks of CKD-MBD is secondary hyperparathyroidism. Besides its well-known expression in bone and kidney, where it directly acts as a regulator of calcium homeostasis, the PTH receptor is also expressed in many other tissues such as the vasculature including aorta, at least in animals [62]. Therefore, it is conceivable that it may directly affect vascular properties and function, and be involved in the effects of calcium as described previously. As it is for vitamin D, it may be difficult to distinguish direct effects of PTH on arterial stiffness from indirect effects mediated by changes in especially serum calcium concentrations, or PTH-induced hyperphosphatemia in advanced CKD, which then would promote VC.

Early studies showed that PTH had acute vasodilatory properties, pointing to an effect on resistance in arteries. However, the acute infusion of PTH in healthy volunteers in one arm, using the other arm as control, did not influence endothelial cell function [63]. A different effect was found following the subacute infusion of PTH (over 2 hours) in healthy young man, where an increase of blood pressure was found [64]. This was accompanied by an increase in intracellular calcium, which suggested that calcium influx in cells was responsible for the effects on blood pressure.

Observations made in people with primary hyperparathyroidism (pHPT) may serve as a “cleaner” model of its vascular effects than the situation of secondary HPT (sHPT), where many additional metabolic derangements of CKD and hypertension can confound effecta on arterial stiffness. In this regard, it is noteworthy that a recent meta-analysis addressing the effects on PWV of sHPT and subsequent parathyroidectomy supported a direct role for PTH as inducer of arterial stiffness [65]. The results of this analysis, however, cannot serve as a final proof of a direct effect of PTH, because in general calcium control is much better after the intervention.

Several studies examined the effects of treatments for sHPT on arterial stiffness, mainly by either the oral calcimimetic cinacalcet or surgical parathyroidectomy. Obviously both interventions will also change phosphate and calcium homeostasis, besides changing bone metabolism, all of which could have affected arterial properties including stiffness. In addition, cinacalcet acts on the calcium sensing receptor, which is also expressed in the vasculature, as pointed out [66]. Therefore, effects of a calcimimetic, if any, may be directly by this mode of action and not mediated by PTH reduction. Indeed, in a small observational study among HD patients treated for 12 months with cinacalcet, PWV improved from 9.35 ± 1.83 m/sg to 8.66 ± 1.86 [67], while in general PWV deteriorates over time. As with phosphate, this effect may be mediated by retarding the progression of VC, a virtue of cinacalcet that was demonstrated in the ADVANCE trial [68]. In a larger open label study, dialysis patients were randomized to standard of care for sHPT or a regimen that contained cinacalcet, with the same biochemical goals of treatment for both arms [69]. Both arms attained comparable control of phosphate and PTH, which improved substantially in both. However, there was no within-group difference compared to baseline for PWV, and no difference between treatment arms. This argues against a major effect of PTH on arterial stiffness in a hemodialysis population. In turn, one might argue that preventing deteriorating PWV over 1 year in this population is meaningful.

The interpretation of a short-term study of cinacalcet might be less distorted by the factor time and progression of VC due to structural changes. However, after 1 week of cinacalcet treatment in people with hemodialysis dependent CKD, despite a substantial reduction of PTH and ionized calcium, no change in PWV was observed [70].

Findings from studies performed in people treated by PD are essentially the same as in hemodialysis-treated individuals. In a small observational study in PD, patients treated by cinacalcet for 1 year had no change of PWV, despite a 60% reduction of PTH [71]. In a recent study, PD patients with uncontrolled sHPT were randomized to treatment with cinacalcet or underwent parathyroidectomy [72]. In both groups, PWV did not change over time and there was no between-group difference, despite substantial reductions in PTH, calcium, and phosphate.

Taken together, the evidence that PTH has a direct effect on arterial stiffness is weak, and likely negligible in people with advanced CKD. In turn, uncontrolled sHPT, with the simultaneous existence of high serum phosphate concentrations, may contribute to VC, which subsequently aggravates arterial stiffness.

Other components of CKD-MBD and pulse wave velocity

Increasing knowledge on CKD-MBD has expanded the number of metabolites that can be considered to be belonging the realm of the syndrome. In recent years, the role of magnesium has gained attention and it may have effects on properties of the arterial tree. This is supported by a recent meta-analysis that established that a higher serum magnesium concentration consistently was associated with improved clinical outcome for different stages of CKD and for a range of clinically relevant endpoints [73]. Long-term magnesium citrate supplementation indeed improved cfPWV in a randomized placebo-controlled trial among individuals with a high cardiometabolic risk profile [74]. Because magnesium was provided as a citrate salt, it was not excluded that calcium chelation by citrate mediated the beneficial effects. Therefore, the same researchers, in another trial, tested different formulations of magnesium salts [75]. Here, no effects on PWV were observed, which provides an argument for the role of calcium on PWV. With regards to magnesium, more intervention studies are needed, especially in high-risk populations.

Another major novel member of CKD-MBD is FGF23. In experimental studies, it was shown that FGF23 directly impairs vasodilation in small resistance arteries by unexplored mechanisms [76, 77]. In a small ($n = 40$) prospective observational study, CKD appeared to be in line with the assumption of vascular effects of FGF23 [78]. Among people with CKD stage 4 it was found that baseline FGF23 was associated with PWV and progression of PWV [78]. This was not confirmed by other studies. An earlier observational study in people with CKD stages 3–4, using augmentation index derived from pulse wave analysis as indicator of arterial stiffness, did not find an association with FGF23. It did find association with established risk factors for stiffness (age, female gender, black race, and systolic blood pressure), which supports the validity of the methods used. By far the largest observational study was an analysis from MESA among 5977 participants. Here also arterial stiffness was estimated from pulse wave analysis derived from the radial artery. There was no association of FGF23 with arterial stiffness, and results were the same for those with an eGFR <60 ml/min. This absence of association of FGF23 with arterial stiffness was in line with a study among people with variable degrees of CKD [79, 80].

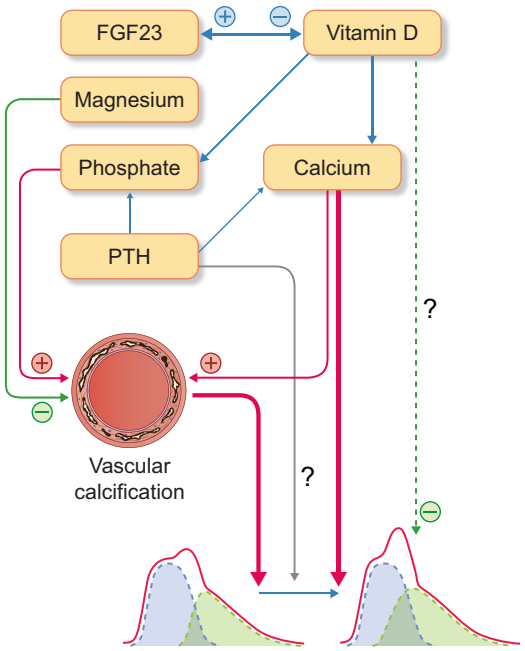

Figure 4: Effects of CKD-MBD biomarkers on arterial stiffness. Calcium directly increases arterial stiffness and contributes to vascular calcification, indicated by red arrows. There is weak evidence that vitamin D improves arterial stiffness. In primary hyperparathyroidism studies support a role for PTH on artrial stiffness, but this is not shown in CKD, indicated by the yellow arrow. The effects of phosphate are most likely all mediated by vascular calcification, while the effects of magnesium are mediated by inhibiting calcification. There are no data that show effects of FGF23 on arterial stiffness.

- There are no data that show direct effects on arterial stiffness of serum phosphate, PTH, magnesium or FGF23 concentrations.
- Higher PTH, phosphate, and lower magnesium concentrations may accelerate VC, thereby worsening arterial stiffness.
- Data regarding the effects of calcifediol on arterial stiffness are inconclusive.
- The apparent benefits of lower serum calcium on arterial stiffness, must be balanced with the risks of hemodynamic instability during hemodialysis, and a negative calcium balance that may affect bone health.

CONCLUSIONS

Most components of CKD-MBD as described here do not have a direct effect on arterial stiffness. The one exception is serum calcium (Fig. 4). Higher levels of calcium, also within the normal range, worsen arterial stiffness, which can clinically be measured by increased PWV. This effect is independent from its potential contribution to VC. This finding seems be in line with a recent analysis from a large European dialysis cohort where the optimal calcium concentration was in the low-normal range [81]. It is uncertain whether these findings should change clinical practice for two reasons. First, arterial stiffness is an intermediate endpoint, and it is uncertain whether improving it in people with CKD will improve clinical outcome. Second, strategies restrictive on calcium may induce a negative calcium balance with implications for bone, and induce more hypotensive episodes for people treated by hemodialysis. Therefore, treatment should be individualized, taking these aspects into consideration.

The absence of direct effect on arterial stiffness of the other CKD-MBD biomarkers should not induce reluctance to optimize their control. For several of these, it is well established they can contribute to VC, an aspect that was beyond the scope of this review.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article.

CONFLICT OF INTEREST STATEMENT

None declared.

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