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NDT Perspectives

Vascular calcification in chronic kidney disease: are biomarkers useful for probing the pathobiology and the health risks of this process in the clinical scenario?

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ABSTRACT

Patients with chronic kidney disease (CKD) are at a particularly high risk for cardiovascular disease. Vascular calcification (VC) is considered a cardiovascular risk marker, so in CKD patients screening for the presence of VC is suggested in current guidelines. VC is the result of both passive and active processes that involve a variety of proteins and factors. In the CKD population, numerous studies have identified circulating biomarkers potentially responsible for VC and have evaluated their link with this process. This narrative review, and an accompanying analysis performed on the Amiens CKD database, focuses on selected VC biomarkers—namely phosphate, fibroblast growth factor 23 (FGF23), osteopontin (OPN), osteoprotegerin (OPG), matrix Gla protein and fetuin A—all of which have been implicated as major players in VC in experimental studies *in vitro* or in animal models. None of the VC biomarkers considered in this review have qualified as a reliable predictor of meaningful clinical events or as a valid indicator of the risk of having VC. In the analysis based on the Amiens-CKD database, no biomarker outperformed age and the classical risk factors as a predictor of VC either in the aorta or in the coronaries. Well-designed clinical trials are now urgently needed to test the potential value of these biomarkers as a guide for interventions targeting VC.

Keywords: biomarkers, chronic kidney disease, vascular calcification

INTRODUCTION

Vascular calcification (VC) is highly correlated with cardiovascular morbidity and mortality, and linked to ageing,

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diabetes and chronic kidney disease (CKD) [1]. The prevalence of VC increases steadily through the stages of CKD peaking in CKD Stage 5D patients [2]. VC is currently considered as a cardiovascular risk marker; the presence of VC has been associated with a several-fold increase in the risk of morbidity and mortality in both the general population and CKD Stage 5D patients [3]. Indeed, the *Kidney Disease Improving Global Outcomes* international clinical practice guideline suggests that CKD Stage 3–5D patients with known vascular/valvular calcification (VC) need to 'be considered as having the highest possible cardiovascular risk' [4]. VC results from both passive and active processes implicating a variety of mediator and effector proteins. Undoubtedly, precipitation of calcium salts in the vessel wall and biologic events at the cell level leading to vessel 'ossification' represent relevant steps in vascular damage induced by various diseases, from metabolic diseases like diabetes and hypercholesterolaemia to CKD itself [5]. However, it is still not completely clear whether calcification is a protective or deleterious event in the evolution of arterial disease [6]. Therefore, the identification of circulating biomarkers of this process and systematic testing of their links with VC and subsequent clinical events is of paramount importance for advancing knowledge in this clinical research area. Several molecules may potentially serve as biomarkers for understanding pathophysiological mechanisms underlying VC and the evolution over the time of the same pathomechanisms. This narrative review is a precis of potential biomarkers of VC that have been shown to be (i) correlates and/or predictors of VC in clinical studies and (ii) have solid background experimental data, documenting that they are direct, causal, players in VC in experimental models. An initial list of selected clinical studies evaluating the relationship between phosphate and a restricted set of emerging VC biomarkers [fibroblast growth factor 23 (FGF23), osteopontin (OPN), osteoprotegerin (OPG), matrix Gla protein, fetuin-A, magnesium and pyrophosphate (PPi)] was prepared by S. L. and Z.A.M. This list was then integrated with additional studies suggested by the panel of EURECA-m investigators. The final list (Supplementary data Appendix S1) was established by consensus through two discussion runs and includes studies focusing on biomarkers deemed to be relevant to the understanding of VC and for the health risk associated and/or predicted by the same biomarkers. Since the discriminant power of VC in studies in CKD patients has only sparsely been tested and since there is no comparative study of the discriminant power of the VC biomarkers in CKD, we took the opportunity to perform such an analysis in the Amiens-CKD database, a database including state-of-the-art quantification of VC by multislice computed tomography [7] as well as comprehensive measurements of the reviewed biomarkers of VC.

Phosphate

Phosphate is one of the most investigated biomarkers in CKD patients. Higher serum phosphate concentrations have been consistently associated with cardiovascular events and mortality in a large series of cohort studies in CKD patients and in subjects with normal kidney function [8, 9] and a meta-analysis documented a strong, independent association between the serum levels of phosphorus and the risk of death in the CKD population [10]. VC represents an intriguing candidate mechanism for linking phosphate accumulation with cardiovascular risk. *In vitro*, phosphate acts directly on cultured vascular smooth muscle cells and initiates phenotype transformation (characterized by loss of contractility, the expression of bone-specific markers and calcification of matrix proteins [11, 12]) leading to VC. Phosphate levels >6 mg/dL directly promote robust calcification, whereas lower concentrations might still initiate calcification *in vivo* in the presence of other synergistic factors [13, 14], including plasma calcium concentration. In CKD patients, epidemiological studies have demonstrated a link between high serum phosphate concentrations and vascular/valvular calcification [15, 16]. In addition, evidence from uraemic animal models suggests that calcium-free phosphate binders slow down the progression of VC [17–19]. This has been confirmed in various clinical trials performed in haemodialysis patients [20–22]. It is noteworthy that an independent link between high-normal phosphate levels (but still within the normal range) and valvular calcification was observed in a recent study of a population-based cohort of 1983 older non-CKD adults [23]. Thus, experimental and epidemiological data coherently point to an association between phosphate and VC, while a clinical trial with a calcium-free phosphate binder indicated that phosphate is a modifiable risk factor for mitigating the progression of coronary calcification in haemodialysis patients [20, 22]. However, the clinical implication of this trial for the prevention of the high risk for cardiovascular events in this population remains unclear because the primary analysis of a full-scale clinical trial failed to show a benefit of the same phosphate binder on mortality and other clinical end points [24]. In a randomized multicentre pilot study on 212 CKD Stage 3 and 4 outpatients, *de novo* onset of coronary artery calcification (CAC) was significantly inferior in sevelamer group compared with calcium carbonate group, and 24 patients treated with sevelamer have a significant regression of CAC score against 2 patients in calcium carbonate group [25]. However, the implications of this study remain difficult to interpret in terms of health outcomes because there was no significant reduction in all-cause mortality with sevelamer hydrochloride as compared with calcium-based agents in a meta-analysis encompassing 10 studies and 3079 patients [26]. However, a recent pilot study in pre-dialysis CKD patients testing the effect of several phosphate binders on VC has shown that a 22% reduction in phosphate load by these drugs is associated with an unexpected increase in VC in this population [27]. Even though this trial had major methodological issues [28], the fact remains that serum phosphate cannot be taken as an unambiguous indicator of the risk of VC and that this biomarker should be interpreted in a context including full information on major hormonal factors regulating mineral balance such as FGF23. Indeed, the extent to which phosphate concentrations would have to be corrected is not known and serum phosphate may not be the ideal marker of the phosphate load (especially in early CKD stages, see below).

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FGF23

FGF23, a phosphaturic hormone produced by osteoblasts and osteocytes, and the associated co-receptor, Klotho, form a complex which is a major regulator of mineral metabolism [29]. Abrogation of the FGF23 gene in the FGF$23^{-/-}$null mice produces a phenotype characterized by hyperphosphataemia, high 1.25 (OH)2 vitamin D and excessive calcification in the abdominal aorta [30], suggesting that the lack of FGF23 and the ensuing hyperphosphataemia and associated metabolic alterations have a major role in VC. Recently, Shalhoub *et al.* showed that in the rat, the neutralization of FGF23 by a specific monoclonal antibody was associated with an increase in aortic calcification and a greater risk of mortality [31]. On the other hand, abrogation of the fundamental FGF23 co-receptor, Klotho (Klotho$^{-/-}$ mice), an experimental model associated with the presence of very high FGF23 levels, is also associated with an identical phenotype, including severe VC [32, 33].

Indeed, in patients at Stage 5D, the plasma concentration of FG23 is at least 20 times higher than the upper limit of the normal range in healthy individuals. Elevated FGF23 is an independent risk factor for end-stage renal disease in patients with relatively preserved kidney function and for mortality across the spectrum of CKD [34, 35]. This increase of FGF23 in CKD, particularly in Stage 5D, mainly reflects augmented synthesis of the agonist in the presence of resistance at the receptor level because Stage 5D is a condition of profound Klotho deficiency [36]. Therefore, Stage 5D represents a unique human model to probe the effect of high FGF23/low Klotho on VC. Circulating FGF23 in CKD Stage 5D patients in haemodialysis has been associated with the severity of aortic calcification (as evaluated by non-contrast computed tomography) [37], peripheral arterial calcification [38], as well as with progression of aortic calcification [39]. The association between aortic calcification and FGF23 levels has been recently confirmed in a survey in patients with CKD of various severity [40]. Thus, with the exception of one small study [41], the association between FGF23 and VC seems to be a consistent finding at all stages of CKD. Intriguingly, well beyond CKD, a strong link between FGF23 and vascular (aortic) calcification was reported also in a large survey ($n = 1130$) in the general population [42], generating the hypothesis that a condition of Klotho resistance and/or a (hitherto unknown) direct pro-calcifying effect of FGF23 may exist also in the presence of normal renal function. In this regard, inflammatory cytokines decrease renal Klotho expression in mice with normal renal function [43, 44]. In contrast with aorta and peripheral arteries, the relationship between FGF23 and intimal coronary calcification (reflecting atherosclerosis rather than arteriosclerosis) is inconsistent across available studies [40, 45, 46]. Yet, in the largest study performed so far in predialysis CKD patients ($n = 195$), FGF23 was one of the strongest biomarkers of CAC [47]. In the majority of reports, FGF23 has been directly linked to VC in general and aortic calcification in particular. In contrast, a recent report on 1501 patients from the chronic renal insufficiency cohort failed to show any association between plasma FGF23 and CAC [48]. The fact that the blood sample for FGF23 evaluation and the computed tomography to evaluate calcification were not synchronous is an inherent limitation of this large cross-sectional analysis. Future studies measuring also serum Klotho levels will clarify the relative role of FGF23 and Klotho in VC in humans. Circulating Klotho levels were unrelated to kidney function and did not predict clinical events in CKD patients in a very recent study [49]. However, the relevance of circulating Klotho levels needs to be adequately defined. Serum Klotho concentrations may not reflect tissue Klotho concentration [50]. Whether FGF23 may represent a potential therapeutic target for preventing VC remains an open question. FGF23 reduced in some studies after interventions with phosphate binders [51], likely due to retention attributable to reduced renal function, largely failed to re-attain the normal range [27]. Furthermore, FGF23 levels can be decreased by the use of dietary phosphate restriction alone [52] or in combination with phosphate binders [53].

OPN

OPN, a 314 aminoacid matricellular protein [54], is synthesized in various tissues and organ systems, most intensively in bone and epithelial cell lines [55]. In gene-knockout models, OPN deficiency leads to a much greater propensity to mineralize subcutaneously implanted glutaraldehyde-fixed aortic valve leaflets (relative to wild-type animals) [56]. The identification of OPN as a component of the human atherosclerotic plaque (which is highly upregulated in symptomatic carotid atherosclerosis [57] and in calcified coronary plaques [58]) suggests that this protein has a role in atherogenesis and could be a valuable VC marker. Studies in patients with coronary heart disease showed that overexpression of OPN associates in a direct fashion with the presence and extent of atherosclerotic plaques [59] and with calcified lesions in the aorta [59, 60], suggesting that progressively higher plasma levels of this protein in conjunction with a rising calcification burden may underlie a counter-regulatory process aimed at limiting calcium accumulation and ossification of the arterial system. Similarly, OPN was an independent direct correlate of mitral annular calcification and aortic valve sclerosis in 120 stable angina patients [61]. However, no significant difference, in OPN levels were observed among intermediate-risk, asymptomatic patients with and without coronary calcification [62]. Similarly, plasma OPN levels were unrelated to the presence and extent of coronary calcification in patients with established coronary artery disease [63]. With the exception of a small survey in haemodialysis patients [64], studies in CKD patients have failed to show an independent association between circulating OPN and the extent of aortic and coronary calcifications [63, 65]. The poor association between OPN and vascular disease may depend on the fact that phosphorylation of OPN is a prerequisite for this protein exerting an inhibitory effect on VC [66]. Currently available OPN assays do not distinguish between phosphorylated and non-phosphorylated forms.

In conclusion, OPN is a multifunctional protein with complex regulatory functions, some of which influence VC. However, serum OPN is a weak biomarker of VC in CKD

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patients and therefore, it appears unsuitable to probe VC in mechanistic and prognostic studies in man.

OPG

OPG is a soluble protein of the tumour necrosis factor (TNF) receptor superfamily and is classified as an osteoclastogenesis inhibitory factor [67]. Endogenous OPG promotes mineralization in skeletal bone but prevents mineralization in vascular tissues [68]. Importantly, OPG is a decoy receptor for the receptor activator of nuclear factor-kB ligand (RANKL) a fundamental mediator of osteoblast maturation. Accordingly, neutralization of RANKL by OPG impairs osteoclastogenesis at both the bone and vascular levels [69].

In vivo, OPG-deficient mice exhibit medial calcification of the aorta and renal arteries. As remarked for OPN, in human studies in various diseases, including type-2 diabetes, circulating OPG associates directly with VC, particularly so with coronary calcification [70–73] again suggesting a counter-regulatory process aimed at attenuating VC. Similarly, independent positive associations between OPG and CAC [74] in CKD patients and between OPG and aortic calcification [75] and progression of coronary calcification [76] in haemodialysis patients have been reported.

As briefly alluded to, ligands of OPG, like the above-mentioned RANKL, and the TNF-related apoptosis ligand (TRAIL) [67] have a role in the VC process. Studies in CKD patients showed that, independently of VC, low RANKL levels signal an excessive risk for cardiovascular events [77], and that there is no correlation between serum TRAIL levels and VC [78]. Further studies are needed to elucidate the link between OPG and its ligands RANKL and TRAIL and VC and to assess whether alterations in this system may translate into clinically relevant phenomena.

Matrix Gla protein

Matrix Gla protein (MGP) is a 10-kDa protein produced by chondrocytes and vascular smooth muscle cells [79–81]. MGP acts as a calcification inhibitor—probably by directly inhibiting calcium precipitation and crystallization and by interfering with bone morphogenetic protein-2 [13, 82–84]. Mice lacking MGP show intense medial calcification and die prematurely from spontaneous rupture of the calcified vasculature [85]. Gamma-carboxylation by a vitamin K-dependent reaction is a fundamental step for the activation MGP and for this protein inhibiting the calcification process. Furthermore, phosphorylation is needed for MGP secretion and full activation [73–75]. Impaired carboxylation of MGP is associated with both intimal and medial calcification [86], and such an alteration has been implicated in medial VC in dialysis patients [87], a population with profound vitamin K deficiency [88].

Several isoforms of MGP exist: total uncarboxylated MGP (t-ucMGP), dephosphorylated uncarboxylated MGP (dp-ucMGP) and dephosphorylated carboxylated MGP (dp-cMGP). To date, no biochemical assay for the fully mature, circulating MGP (including both the carboxylated and phosphorylated forms) is available. Studies in haemodialysis patients show an inverse association between t-ucMGP levels and VC [89–91]. Results in non-CKD populations are conflicting [84, 92–94], which may be related to the fact that t-ucMGP levels in these studies were measured with a monoantibody assay which was insensitive to MGP phosphorylation status. Phosphorylated and dephosphorylated MGP fraction effects on the progression of VC may differ. Dephosphorylated carboxylated MGP levels increase progressively with CKD stage and associate with the severity of aortic calcification [95]. Plasma levels of both dephosphorylated uncarboxylated (dp-ucMGP) and dephosphorylated carboxylated MGP (dp-cMGP) are increased in haemodialysis patients [87]. Of note, vitamin K2 supplementation in a small group of HD patients significantly reduced dp-ucMGP levels [88, 96]. Moreover, supplementation with vitamin K1 for 3 years halted the progression of coronary arterial calcification in a study in healthy, elderly adults [97]. Overall, interference with vitamin K compounds or disturbed regulation of MGP appears to be a promising intervention to limit VC. However, MGP assays that distinguish the various isoforms need to be developed to further test the potential of this biomarker in clinical research.

Fetuin-A

Fetuin-A (also known as α2-Heremans Schmid glycoprotein) is an abundant serum glycoprotein produced in the liver (molecular weight, ∼60 kDa). When taken up by vascular smooth muscle cells, fetuin-A reduces the calcification of matrix vesicles [98, 99]. The relevance of fetuin-A as a calcification inhibitor is epitomized by the observation that fetuin-knockout mice develop extensive ectopic calcification when fed a phosphorus- and vitamin D-enriched diet. To note, the fetuin A gene knock out is combined with a DBA/2 genetic background (associated with hereditary hypomagnesaemia) [100].

Low serum fetuin-A concentration is inversely associated with the presence of VC in CKD Stage 5D dialysis patients [73, 101–103] and in patients with type-2 diabetes and coronary heart disease [104–106]. However, no such relationship was found in two studies in patients with diabetic nephropathy [107, 108]. It was hypothesized that the discrepancy depends on the fact that serum fetuin-A in CKD patients is mainly present as a fetuin-mineral complex (FMC, composed of fetuin-A, fibrinogen, fibronectin-1 and calcium) rather than in free form. Indeed, the fraction of total fetuin-A as FMC increases progressively as the glomerular filtration rate decreases and serum levels of FMC, but not of fetuin-A in its free form, associates with the CAC score in diabetic pre-dialysis patients [109]. This observation still needs to be replicated in other studies. Overall, at this stage of knowledge circulating fetuin-A appears to be just a weak correlate of VC and measurement of this biomarker in clinical practice is unwarranted.

Magnesium

Magnesium acts as a cofactor in many enzyme reactions; it has a role in maintaining cardiac rhythm and modulating mineral metabolism and (potentially) the calcification process. Several *in vitro* studies have shown that magnesium can have an inhibitory effect on hydroxyapatite formation and precipitation, as well as on calcification [110]. Recently, Louvet *et al.*

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showed that elevated magnesium concentrations reduced phosphate-induced calcification in human aortic vascular smooth muscle cells [111]. The results of several animal studies have demonstrated that changes in the dietary intake of magnesium can variously cause or prevent VC [112–114].

In patients on dialysis, a number of observational studies have linked low serum magnesium levels to an increase of peripheral arterial calcification [115], mitral annular calcification [116] and intima-media thickness [117]. Patients with slightly elevated magnesium levels may have a survival benefit, whereas low magnesium levels have been associated with mortality in patients on dialysis [118]. Interestingly, in a pilot study including seven chronic haemodialysis patients, long-term administration of oral magnesium supplements might retard arterial calcification [119]. So, it is important to confirm the clinical interest of magnesium supplementation in CKD setting.

PPi

PPi is a major inhibitor of hydroxyapatite formation and VC [120]. Plasma PPi levels may be abnormally low in haemodialysis patients [121]. O'Neill *et al.* studied different types of CKD patients (Stage 4, haemodialysis and peritoneal dialysis) and showed that plasma PPI is negatively correlated with VC [122]. In animal models, daily peritoneal administration of sodium PPi was able to prevent the development of aorta calcification [123, 124].

Do circulating biomarkers hold discriminative power for VC?

In the Amiens-CKD database, 131 patients at different CKD stages (11 at Stage 2, 33 at Stage 3, 36 at Stage 4, 8 at Stage 5 and 43 at Stage 5D) had simultaneous multislice computed tomography (MSCT) evaluation and measurements of the plasma concentrations of all putative VC biomarkers dealt with in this review. The study population, described in detail elsewhere (2), was predominantly composed of males (62%), with a mean age of 67 ± 12 years. The mean aortic calcification and coronary calcification scores were 3.0 ± 3% and 591 ± 1230 Agatston units, respectively. We took the almost unique opportunity offered by this database to evaluate the biomarkers' ability to identify individuals with VC (defined as an Agatston score >17 AU for coronary calcification and >0.75% for aortic calcification, the cut-offs of 17 AU and 0.75% corresponded to the first quartiles of the coronary calcification score and the aortic calcification score, respectively) and to measure the discriminative ability added by each of these biomarkers to a simple predictive model based on the age and classical risk factors [diabetes, smoking status, low density lipoprotein (LDL) cholesterol, systolic BP, sex]. The correlation coefficients of the individual relationship of each biomarker with VC in the aorta and in coronary arteries are reported in Table 1. Only FGF23, OPG and dp-ucMPG were related to VC. Importantly, such relationships were fairly weak because these biomarkers explained (r^2) just a small proportion (4.2–16.1%) of the variability of VC in unadjusted analyses.

The unadjusted discrimination power for aortic calcification of biomarkers [area under the receiver operating characteristic (ROC) curve, area under the curve (AUC)] and the corresponding sensitivity, specificity is shown in Table 2 and Figure 1. Among biomarkers considered in this study, only dp-ucMGP levels (AUC 0.76; 95% CI, 0.64–0.88, P < 0.0001) and FGF23 levels (0.63; 95% CI, 0.52–0.75, P = 0.02) hold

Table 1. Correlation between studied biomarkers and aortic calcification/coronary calcification

	Aortic calcification (Ln)		Coronary calcification (Ln)	
	r (P)	$r^2 \times 100$	*r* (P)	$r^2 \times 100$
Phosphate (Ln)	0.009 (0.921)	0.008	0.091 (0.427)	0.8
FGF23 (Ln)	**0.20 (0.019)**	**4.2**	**0.20 (0.031)**	**4**
OPN	0.06597 (0.545)	0.4	−0.036 (0.80)	0.1
OPG (Ln)	**0.21 (0.03)**	**4.4**	**0.278 (0.03)**	**7.7**
dp-ucMGP	**0.401(<0.0001)**	**16.1**	**0.320 (0.02)**	**10.2**
Fetuin A	0.001 (0.995)	0.0001	0.026 (0.823)	0.07

r, Pearson's coefficient; FGF23, fibroblast growth factor 23; OPN, osteopontin; OPG, osteoprotegerin; dp-ucMGP, dephosphorylated uncarboxylated Matrix Gla protein; Ln, log normalized.
Bold value represent significance.

Table 2. Unadjusted discrimination power of biomarkers for prediction of vascular calcification (VC) in the aorta

	AUC	95% CI	P	Optimal Cut off	Sensitivity	Specificity
Age	0.877	0.809–0.946	<0.0001	65.5 years	0.724	0.868
Phosphate	0.498	0.383–0.614	0.979			
FGF23	0.634	0.517–0.751	0.02	31.07 pg/mL	0.704	0.606
OPN	0.600	0.416–0.783	0.203			
OPG	0.619	0.487–0.751	0.07			
dp-ucMGP	0.758	0.635–0.881	<0.0001	666.1 pM	0.720	0.789
Fetuin A	0.516	0.392–0.640	0.785			

FGF23, fibroblast growth factor 23; OPN, osteopontin; OPG, osteoprotegerin; dp-ucMGP, dephosphorylated uncarboxylated matrix Gla protein. AUC, area under the curve.

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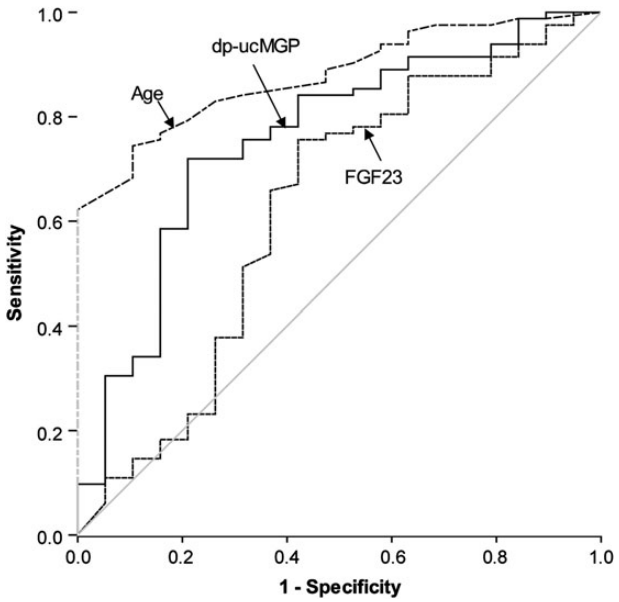


FIGURE 1: ROC curves for risk factors for aortic calcification. The areas under the ROC curves are 0.87 [95% confidence interval (CI), 0.81–0.95, P < 0.0001), 0.76 (95% CI, 0.64–0.88, P < 0.0001) and 0.64 (95% CI, 0.52–0.75, P = 0.02) for age, uncarboxylated, dephosphorylated Matrix Gla protein (dp-ucMGP) and fibroblast growth factor 23 (FGF23), respectively. Phosphate, OPN, fetuin-A and OPG levels were not found to be potential predictors of aortic calcification.

significant discriminative power. Phosphate, OPN, fetuin A and OPG levels failed to identify patients with aortic calcification in this database. Age was the risk factor holding the greatest discriminative power (AUC 0.88; 95% CI, 0.81–0.95, P < 0.0001) and addition of sex, diabetes, smoking status, LDL cholesterol, systolic BP, to the age-based logistic model further increased the discriminative power of the same model (AUC: 0.93; 95% CI, 0.86–0.96 P < 0.0001).

For coronary calcification, the AUCs were significant for age (0.69; 95% CI, 0.553–0.836, P = 0.023), OPG levels (0.69; 95% CI, 0.54–0.84, P = 0.016) and dp-ucMGP levels (0.67; 95% CI, 0.51–0.83, P = 0.046), whereas phosphate, OPN, fetuin-A and FGF23 levels failed to discriminate patients with coronary calcification. Hence, in this particular cohort, dp-ucMGP appeared to be the best biomarker for both aortic and coronary calcification, while FGF23 was a weak biomarker of aortic calcification only. Although dp-ucMGP and FGF23 had a weak to moderate discrimination power for VC, neither of these biomarkers individually or combined with other biomarkers added discriminative power to the logistic model based on the age and classical risk factors (Figure 2). Thus, biomarkers did not outperform age and classical risk factors as a predictor of calcification either in the aorta or the coronaries. Thus, in clinical practice CKD patients with VC can be effectively identified only on the basis of age and classical risk factors.

New approaches-perspectives

Whether global methods such as proteomic studies may serve to refine discrimination of CKD patients with VC remains to be explored [125]. In addition, Pasch *et al.* recently developed a nanoparticle-based test that could measure the overall propensity for calcification in serum [126]. However, the clinical relevance of this test needs to be confirmed in large studies.

CONCLUSION

VC is a powerful risk marker in CKD patients, but the biologic phenomena underpinning this process remain incompletely elucidated. Furthermore, we are still unclear whether this alteration represents a noxious mechanism aggravating vascular damage or a protective phenomenon aimed at attenuating vascular damage by various offending factors [4]. The results of the ongoing search for biomarkers of VC suggest that aortic and coronary calcifications have differing specificities at least partially. In part, the discrepant results generating in the field of VC might arise from the heterogeneity of VC (i.e. media versus intima) and

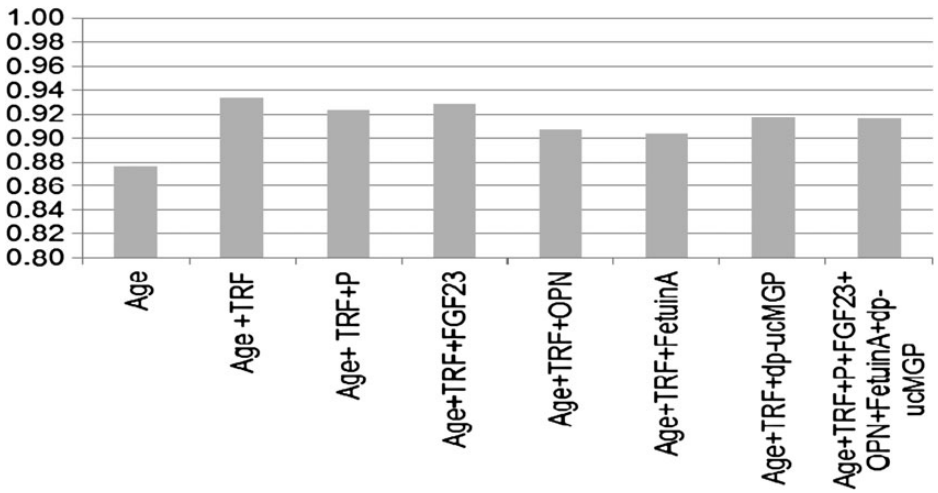


FIGURE 2: Influence of adjustment for age, traditional risk factors (TRFs) (including diabetes, smoking status, LDL cholesterol, systolic BP, sex), phosphate (P), fibroblast growth factor 23 (FGF23), OPN, Fetuin A, matrix Gla protein (MGP) on the area under the curve predicting aortic calcification.

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the limitation of imaging that cannot distinguish among these two forms of VC. Age is a preponderant factor correlated with both the types of VC in all clinical studies. In the Amiens cohort, biomarkers did not outperform age and traditional risk factors in predicting aortic calcification. Thus, identification of CKD patients' aortic VC can presently be accomplished without the measurement of VC biomarkers. Whether global methods such as proteomic studies may serve to refine discrimination of CKD patients with VC remains to be explored [125, 126]. Although the VC biomarkers tested in the Amiens database were only weakly related to radiological VC and largely failed to add meaningful information for discrimination of CKD patients with coronary and/or aortic calcification, the possibility remains that they may be useful for monitoring interventions aimed at preventing or mitigating VC. For example, at least in theory, FGF23 may serve to monitor interventions aimed at reducing phosphate burden in CKD, while dp-ucMGP levels may be exploited to monitor vitamin K interventions in the same population (see above). Clearly, well-designed clinical trials are needed to test the value of these biomarkers as a guide for interventions targeting VC. Furthermore, substantial questions loom large in this research area. Foremost, the very basic question whether VC represents a valid treatment target in CKD patients is still unanswered. This question should be an absolute priority if we are to effectively tackle the burden of CV disease in the high-risk CKD population.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

S.L., H.O., L.D., A.O., G.S., F.M., C.Z. and G.L. had nothing to declare. D.F. declares being consultant for Abbott, Amgen, FMC, Janssen-Cilag, Roche, Red Flag Diagnostics, FGF-23, and also declares having received speaking fees for Abbott, Amgen, Berlin-Chemie, Daiichi-Sankyo, FMC, Genzyme, Novartis, Roche, Shire. D.G. declares having received speaking honoraria for Sanofi and Amgen. A.C. declares having received speaking fees for Amgen, Abbott and is a consultant for FMC, Affymax. A.W. declares giving expert and scientific advices for Boerhinger Ingelheim, Abbot, Amgen, Vifor, Affyax, Roche, Teva and Fresenus. A.M.C. declares having received Honorarias for conferences by Abbott, Amgen, Boheringer-Ingelheim, Janssen-Cilag, Lilly, Novartis, Roche, Shire and being consultant for Abbott, Amgen, Roche and Esteve. B.L. is employed by Baxter Healthcare Corporation. Z.A.M. declares having received speaking fees and research grants from Amgen, Genzyme/Sanofi, FMC and Baxter.

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Glucose-lowering drugs in patients with chronic kidney disease: a narrative review on pharmacokinetic properties

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ABSTRACT

The achievement of a good glycaemic control is one of the cornerstones for preventing and delaying progression of microvascular and macrovascular complications in patients with both diabetes and chronic kidney disease (CKD). As for other drugs, the presence of an impaired renal function may significantly affect pharmacokinetics of the majority of glucose-lowering agents, thus exposing diabetic CKD patients to a higher risk of side effects, mainly hypoglycaemic episodes. As a consequence, a reduction in dosing and/or frequency of

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