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REVIEW

RAASi, MRA and FGF-23 in CKD progression: the usual suspects?

Giuseppe CIANCIOLO [1], Michele PROVENZANO [2], Lilio HU [3], Simona BARBUTO [1], Maria J. SOLER [4], Paola CICERI [5], Mario COZZOLINO [5], Gaetano LA MANNA [1, 3] *

[1]Nephrology, Dialysis and Kidney Transplant Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [2]Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Cosenza, Italy; [3]Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum – University of Bologna, Bologna, Italy; [4]Nephrology Department, Hospital Vall d'Hebron and Vall d'Hebron Research Institute (VHIR), Barcelona, Spain; [5]Department of Health Sciences, University of Milan, Renal Division, ASST Santi Paolo e Carlo, Milan, Italy

*Corresponding author: Gaetano La Manna, Nephrology, Dialysis and Kidney Transplant Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. E-mail: gaetano.lamanna@unibo.it

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ABSTRACT

Chronic kidney disease (CKD) affects almost 10% of the global population and is a significant health issue. The presence of CKD increases the risk of fatal and non-fatal cardiovascular events, overall mortality, and progression of renal damage leading to kidney failure. Inhibiting the renin-angiotensin-aldosterone system (RAAS) through angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers reduces proteinuria and slows eGFR decline in CKD patients. Several factors can reduce the effect of inhibition RAAS, such as individual variations, drug intolerance, and adverse effects like hyperkalemia. Moreover, the aldosterone breakthrough phenomenon, where aldosterone levels rebound during RAAS therapy, limits treatment efficacy in reducing proteinuria and slowing the progression of CKD and is associated with poor cardiovascular and renal outcomes. Similarly, FGF23 attenuates RAAS blockade effectiveness through, in fact, enhancing the expression of angiotensin-converting enzyme 2 and reducing degradation of angiotensin I to angiotensin 1-9 and angiotensin II to angiotensin 1-7 inducing a reduced efficacy in controlling RAAS-mediated effects and an increase of cardiovascular risk and CKD progression. New therapeutic strategies to reduce the progression of CKD, such as SGLT-2 inhibitors, GLP-1 receptor agonists, and mineralocorticoid receptor antagonists (MRAs), are recommended in CKD patients to reduce the risk of progression and cardiovascular events. Furthermore, these therapies may reduce FGF-23 levels and regulate aldosterone breakthrough. This review aims to clarify the mechanisms underlying CKD progression, with a focus on aldosterone breakthrough, FGF-23, and activins, in order to identify new therapeutic approaches for better management of CKD and its complications.

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Chronic kidney disease (CKD) is defined as abnormalities of kidney function or structure that are present for at least 3 months, whose most common diagnostic criteria are estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and urinary albumin to creatinine ratio (UACR) >30 mg/g.[1] CKD is characterized by a progressive loss of kidney function

and represents an enormous global health problem. CKD affects about 10% of the population worldwide and nearly four million patients require kidney replacement therapy (KRT).[2] The overall increase in burden of CKD is driven by aging, population growth and above all by the increased global epidemic of diabetes, obesity and to a lesser extent hypertension together with the reduction of mortality for cardiovascular causes due to the introduction of statins and improvements of primary prevention strategies.[3, 4] If current epidemiological projections are confirmed it is presumable that these comorbidities may affect the incidence and progression of CKD, with CKD reaching the fifth global cause of death by the year 2040.[5]

CKD in persons with diabetes mellitus develops in 30 to 40% of patients with diabetes and is the leading cause of CKD worldwide.[6]

The presence of CKD exposes the patient to a poor prognosis, which manifests with an increased risk of fatal and non-fatal cardiovascular (CV) events (myocardial infarction, stroke, heart failure, peripheral vascular disease), overall mortality and progression of renal damage towards kidney failure which is defined as the most advanced stage of CKD, needing the recurrence to KRT.

The association of CKD with cardiovascular morbidity and mortality is well established since both increase with CKD progression or at higher degree of albuminuria just as it is known that the cardiovascular burden is amplified by the interaction deriving from the simultaneous presence of CKD and diabetes.[7]

Inhibition of the renin-angiotensin-aldosterone system (RAAS), either through angiotensin-converting enzyme inhibitors (ACEIs), especially in patients with type 1 diabetes and non-diabetic CKD or angiotensin II receptor blockers (ARBs) in patients with CKD with or without diabetes, decreases proteinuria and relents the eGFR decline in patients with proteinuria.[8, 9]

The nephroprotective effect following ACEis and ARBs therapy is mainly observed in patients with CKD and severely increased albuminuria (UACR >300 mg/g) or moderately increased albuminuria (UACR 30-300 mg/g).[10-12]

Although single RAS blockade may reduce the rate of eGFR decline in proteinuric CKD from about 10-12 to 5-6 mL/min/1.73 m^2/year, it still entails a persistent risk of CKD progression, considering that in healthy individuals (over 40 years old) this decline is estimated at around 1-1.5 mL/min/1.73 m^2 per year. More importantly, in all the clinical trials with single RAS blockade carried out in proteinuric CKD, no differences in cardiovascular outcomes or all-cause mortality were evident between treatment groups.[13-16]

Moreover, residual proteinuria may remain on top of RAAS blockade-based therapy. It has been demonstrated that, in patients already treated with RAAS inhibitors and followed by nephrologists, residual proteinuria is present in up to 70% of patients.[17] The impact of residual proteinuria is reflected by less effective long-term renal and cardiovascular protection in individuals with a poor initial antiproteinuric response with documented increased CV and CKD progressions risks, starting from 0.15 g/24 h of proteinuria onwards.

It is possible that RAAS blockade strategies may be suboptimal due to individual variation in response to therapy, drug intolerance or suboptimal dosing aimed to reducing the onset of common adverse effects, such as AKI and hyperkalemia. Another important mechanism that limits treatment efficacy is the increase of serum aldosterone levels during RAAS blockade with all ACEIs or ARBs, the so-called aldosterone breakthrough. Although aldosterone breakthrough phenomenon has been described many years ago, the pathways involved in are not exactly defined.

From 2018, use of an SGLT-2i has been recommended in patients with DM and CKD with an eGFR >30 mL/min per 1.73 m^2 and at least moderately increased albuminuria (microalbuminuria; UACR >30 mg/g) to reduce the risk of progression of CKD, cardiovascular events, or both.[18-20]

Following the emerging new evidences of SGLT2 inhibitors' showing a reduced risk of CKD progression, cardiovascular events, or both,[21] the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommended SGLT2 inhibitors for patients with CKD and type 2 diabetes.[22]

However, in CREDENCE and DAPA-CKD.[21, 23]

However, in CREDENCE and DAPA-CKD, despite both trials involved the combined use of RAS inhibitors and SGLT-2i, CKD progression or kidney failure still occurred in approximately 10% of patients after a median follow-up of approximately 2.5 years.[24]

Despite the relevant benefits of these innovative treatments, an unacceptably high proportion of treated patients remained at risk of renal and cardiovascular events and premature death. These findings constitute the need to identify possible and unexplored pathophysiological pathways and novel approaches aimed at preventing or slowing CKD progression, in patients with CKD and T2D.

Aims of this review is to analyze uncharted mechanisms underlying the progression of renal damage and identify some pathophysiological links that influence the effects of current treatments.

Aldosterone breakthrough

RAS blockers reduce plasma aldosterone levels in the initial treatment phase, but aldosterone levels may later reach or sometimes exceed pretreatment values so limiting their beneficial effects.

The incidence of the aldosterone breakthrough is up to 53% after 1 year of RAAS blockade, depending on the definition used.[25-27] Moreover aldosterone breakthrough is independent of the RAAS blocker dosage and does not differ with ACEI or ARB treatment and is associated with poor cardiovascular and renal outcomes.[28]

The detailed mechanisms of aldosterone breakthrough have not been elucidated. Some studies suggest that aldosterone breakthrough was associated with a greater decrease in sodium intake, SBP, and eGFR.[27] Moranne *et al*. in a *post-hoc* analysis of the AMADEO study aimed to establish the incidence, determinants, and changes associated with aldosterone breakthrough after ARB treatment in patients with type 2 diabetes mellitus, observed that an increase of serum potassium was statistically significantly associated with an increased risk of aldosterone breakthrough[28] while in others studies no association was demonstrated with changes in plasma potassium as well as Ang II levels.[26] In this analysis losartan exposed participants to a higher risk of aldosterone breakthrough than telmisartan (57% of subjects with aldosterone breakthrough were taking losartan *vs*. 43% of patients taking telmisartan). This finding has been related to nycthemeral variations of aldosterone secretion, with higher levels during the night that may be further increased by volume depletion during the day using loop diuretics.[28]

Additional possible mechanisms of aldosterone breakthrough include: 1) aldosterone production via a RAAS-independent mechanism; 2) insufficient ACE inhibition; 3) Ang-II-independent ACE activity; 4) Ang II breakthrough; 5) angiotensin II type 2 receptor activation;[3] and 6) autonomic nervous system.[26]

Indeed endothelins may be a further promoters of aldosterone breakthrough through both endocrine and paracrine mechanisms. Endothelin receptor antagonists have been shown to reduce plasma aldosterone levels in hypertensive patients, but the effect of these molecules was mainly mediated by the RAS, since the decrease in aldosterone levels was associated with a significant lowering of plasma renin activity.[29]

FGF 23 and CKD progression

An interesting feature that could provide more insights into the pathways involved in aldosterone breakthrough is the complex link between RAAS and fibroblast growth factor-23 (FGF-23). FGF-23, an osteocyte-derived hormone, regulates phosphate homeostasis by stimulating urinary phosphate excretion and lowering 1,25-dihydroxyvitamin D levels.[30]

The effects of FGF23 take place through the binding with the FGF receptors (FGFRs) which are expressed in a variety of tissues. There are four different FGFR isoforms (FGFR1-4), the mineral metabolism actions of FGF23 are mediated through FGFR1, which is expressed ubiquitously. The binding affinity of FGF23 to FGFR1 is enhanced by its co-receptor klotho, a membrane-bound protein mainly expressed in the kidney. FGF23 signaling in the heart and liver oc-

curs through another FGF receptor, FGFR4, in a klotho-independent manner.[31, 32]

Elevated plasma levels of FGF23 and reduced circulating levels of cleaved sKL are associated with both left ventricular hypertrophy (LVH) and the progression of CKD.[33]

Plasma FGF-23 level increases early in chronic kidney disease and can be thousands of times higher than baseline when the patient is about to start renal replacement therapy.[34]

Potential pathways through which higher FGF-23 levels may result in CKD progression are not completely clarified. Whether high FGF-23 level fosters or amplifies kidney injury in the setting of CKD is also unknown. Previous studies suggest that FGF-23 may have profibrotic properties, which may contribute to cardiac fibrosis in individuals with CKD and that FGF-23 excess also may increase fibroblast activation during kidney injury resulting in profibrotic signaling.[35-37]

FGF-23 may also indirectly induce CKD progression by means of further several mechanisms.

By stimulating phosphaturia and promoting nephrocalcinosis, FGF-23 may induce renal tubular damage and tubulointersitital fibrosis.[38] Other indirect effects of FGF-23 on the kidney could be mediated by 1,25-dihydroxyvitamin D deficiency, which has been implicated in CKD progression through multiple potential mechanisms, including failure to adequately suppress anti-inflammatory pathways, to downregulate the renin-angiotensin system, and to inhibit myofibroblast activation.[39]

Humalda *et al.* demonstrated in 47 patients with CKD without diabetes but with residual proteinuria that higher plasma FGF-23 levels independently predicted impaired antiproteinuric response to a low-sodium dietary intervention added to background ACE inhibition.[40] Therefore, higher FGF-23 levels are associated with resistance to volume depletion as a strategy to potentiate RAAS blockade leading the authors to hypothesize that FGF-23 could impair sodium balance by promoting sodium retention and increasing blood pressure.[41] In other words, higher FGF-23 levels may be linked to a state of volume overload that can incompletely be counterbalanced by dietary sodium restriction, resulting in more residual proteinuria.[40] Previous studies demonstrated that FGF-23 levels are associated with parameters of volume status as well as with an increased risk of congestive heart failure in patients with CKD.[42, 43]

FGF23 may impair sodium handling through the up regulation of the sodium chloride cotransporter in the distal tubule, thus promoting sodium reabsorption which entails a volume expansion and cardiac hypertrophy.[44]

Moreover, in a prospective observational case-cohort study within the Chronic Renal Insufficiency Cohort (CRIC) Study, carried out on 1135 patients with CKD stages 2 to 4, higher FGF-23 levels, in an analysis adjusted for eGFR and urinary protein-creatinine ratio, are associated with increased risk for requiring KRT.[45]

Two further pivotal effects on the RAAS system suggest additional pathways through which FGF23 attenuates the efficacy of RAAS blockade. First of all, enhanced expression of angiotensin converting enzyme 2 (ACE2), the enzyme that counteracts RAAS activation by degrading both angiotensin I to Angiotensin 1-9 and with more affinity Ang II to angiotensin 1-7 (Ang 1-7), has been found to be altered in patients with CKD and associated with increased cardiovascular risk.[33] Ang 1-7 by its actions on the MAS receptor, opposes the molecular and cellular effects of AngII, this effect is considered the main mechanism that counterbalances the vasoconstrictive, profibrotic and inflammatory actions of RAAS activation and above all of the excess levels of Ang II.[33, 46]

Ang 1-9 exerts direct biological effects in the cardiovascular system, and these effects may be *via* the AT2R.[47]

In CKD, another pathological link points towards the hypothesis of a relevant role of FGF23 in the impairment of the antiproteinuric therapy through its interaction with the RAAS.

It is known that FGF23 release is stimulated by aldosterone and extracellular volume depletion.[30, 48] Aldosterone, which has hitherto been implicated in regulating volume and electrolyte balance in mammals, might as well have a function in bone homeostasis.

Recent experimental data suggest that FGF-23 suppresses renal ACE2 expression, resulting in increased Ang II generation, which could

translate into a higher aldosterone to renin ratio (ARR).[49]

FGF23 acts on renal sodium (Na) handling upregulating the Na chloride cotransporter (NCC) in the distal tubule thereby so promoting Na reabsorption with consequent volume expansion and cardiac hypertrophy.[44]

The interplay between aldosterone and FGF23 is further demonstrated by the increase of both FGF23 and aldosterone levels in Na chloride cotransporter (NCC) null mice (an experimental model of mild volume depletion): while the aldosterone increases following the volume depletion, the consensual high levels of FGF23 declined after treatment with the MRA eplerenone.[50]

The receptors for angiotensin (AT1 and AT2) and aldosterone (MR) are readily expressed in the bone, which is the main site of FGF23 production.[51, 52] Secondary hyperaldosteronism contributes to or even account for the increased serum FGF23 levels in CKD, heart failure, acute renal failure, diabetic nephropathy. Aldosterone acting on mineralocorticoid receptors is a powerful stimulator of FGF23 synthesis, however mineralocorticoid receptor blockers (eplerenone) are effective in reducing FGF23 levels only in pathological conditions (higher aldosterone levels).[50]

Furthermore, while the FGF-23 co-receptor klotho, at least in part, could contribute to higher FGF-23 levels, renal klotho loss also may further impair the deranged sodium homeostasis through promoting hyperaldosteronism. There is evidence for a close link between Klotho and aldosterone regulation: aldosterone significantly decreases Klotho transcription, while upregulation of aldosterone synthase secondary to Klotho deficiency leads to hyperaldosteronism. The mineralocorticoid receptor antagonist eplerenone reverses Klotho deficiency-induced hypertension and attenuates kidney damage.[53]

Activins and CKD

Activins are dimeric polypeptides members of the TGF-b superfamily like inhibins, bone morphogenetic proteins (BMPs) and growth differentiation factors. Activins are widely expressed factors involved in cell differentiation, proliferation and inflammation, activating signal transduction by binding to receptor heteromultimers. Six isoforms have been identified (activins A, AB, B, C, D and E), of which the most abundant is ActA, with a well-defined biological activity, whose role has been analyzed in experimental models and in clinical studies in the field of CKDwell studied in the field of CKD, ActA exerts its biologic functions through binding to a Type II receptor, ActRIIA or ActRIIB.[54, 55]

An increase of ActA in the kidney and in the bloodstream has been observed in several experimental models of renal fibrosis and in human samples. The ActA expression is induced by TGF-b1 or by ActA itself (in a paracrine manner), and promotes cell proliferation, differentiation and collagen I production by renal interstitial fibroblasts, and matrix protein production by mesangial cells.[56]

The role of ActA in renal osteodystrophy, cardiac hypertrophy, vascular calcification and CKD progression was evaluated in experimental models showing that ActRIIA signaling is stimulated in the kidney, in the skeleton and in the vasculature.[57] Enhanced ActA expression was found in several models of insulin-deficient diabetic kidney disease (DKD), as well as in humans. Serum ActA increases as early as CKD Stage 2, well before any significant increase in parathormone (PTH) and FGF23.[58]

In a recent study carried out on 339 patients with biopsy-confirmed kidney diseases multivariable logistic regression analysis revealed a significant association between plasma activin A levels and the extent of tubulointerstitial fibrosis, indeed plasma activin A levels correlate also with adverse outcomes in various kidney disorders.[59] Activin/BMP system increases transcriptional activation and mRNA levels of aldosterone synthase and aldosterone production induced by Ang II and therefore may be involved in the occurrence of cellular escape from aldosterone suppression under chronic Ang II type 1 receptor blockade.[60]

Effect of genetic variability of SGLT2 in T2DM and treatment response to SGLT2 inhibitors

The mechanism of action of gliflozins (SGLT2 inhibitors) is based on the inhibition of glucose

reabsorption in renal tubules with consequent urine loss which leads to significant reduction in blood glucose and Hb1Ac. Mutations in the SGLT2 gene, the solute carrier family 5 member 2 (SLC5A2) on chromosome 16p11.2, affect the expression, localization, and function of the co-transporter SGLT2: rare missense mutations that cause functional defects of SGLT2 are associated to familial renal glicosuria,[61] but common SLC5A2 genetic variants have been suggested to potentially influence glucose homeostasis and the risk of T2D.[62] Single nucleotide polymorphisms (SNPs) within the SGLT2 gene region have been studied with the aim of analyzing the interindividual variability of the response to treatment with SGLT2 inhibitors and their association with T2D, however with some conflicting results.[63]

In their analysis of four SLC5A2 SNPs (rs9934336, rs3813007, rs3813008, rs3116150) genotyped in a Sorb cohort, Enigk *et al*.[62] did not observe any association with T2D risk but they noticed that rs9934336 was associated with reduced glucose and insulin concentrations respectively at 30 and 120 minutes during the oral glucose tolerance test in nondiabetic individuals. The protective effect of variant rs9934336 to T2D risk and its association with reduced HbA1c was confirmed by Drexel e*et al*.;[64] conversely, Klen *et al*. demonstrated that variant rs9934336 was associated with increased HbA1c and fasting glucose levels in T2D patients.[65] On the other hand, in a large study over 2229 subjects at risk for T2D and who were genotyped for six common SLC5A2 SNPs (rs3116149, rs9934336, rs3813008, rs11646054 rs3116650, rs9924771), Zimdahl *et al*. did not find any association with relevant response to empagliflozin in patients with T2D or any association with diabetic-related metabolic traits.[66]

The inconsistent findings of the available studies suggest the need of more evidence of the clinical impact of SGLT2 polymorphisms on the response of SGLT2i treatment.

GLP-1 effect on FGF-23

Several studies have shown that FGF-23 plays a crucial role in DKD and is associated with an increased risk of cardiovascular events and mortality. Yeung *et al.* carried out a study on 310 patients with type II diabetes and eGFR<60 mL/min. During a follow-up period of almost six years, they observed that FGF-23 was associated with a higher risk of mortality (HR 2.78 [95% CI 1.76-4.40]) and major cardiovascular events (HR 1.67 [1.12-2.49]).[67] There are some studies that suggest that anti-diabetic treatments may have effects on FGF-23 levels. Insulin has been shown to reduce the production of FGF23.[68] However, the effects of SGLT2i on FGF23 are unclear and require further investigation.[69]

In a cross-sectional study involving 246 patients who had type 2 diabetes and an eGFR below 60 ml/min, it was found that patients with higher FGF-23 values had lower myocardial blood flow during stress (2.3±0.9 *vs.* 2.7±0.9 mL/min/g, P=0.001) and lower overall myocardial perfusion reserve (2.7±0.8 *vs.* 3.3±1.1, P<0.001). Additionally, these patients had an elevated left ventricular mass (143±40 *vs.* 138±36 g, P=0.04).[70] Interestingly, patients receiving therapy with GLP-1 analogues alone or in combination with insulin had lower FGF-23 values.[70] These findings are consistent with the results of the LEADER study (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results). The LEADER study observed that treatment with GLP-1 analogues had a positive impact on the composite cardiovascular outcome, which includes death due to cardiovascular events, non-fatal myocardial infarction and non-fatal stroke.[71] Additionally, a pooled analysis of the SUSTAIN 6 (Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects With Type 2 Diabetes) and LEADER trials revealed that both semaglutide and liraglutide led to a 24% decrease in albuminuria from the baseline to two years after randomization.[72]

Effect of neprilysin inhibitors (NePi) in CKD

Neprilysin inhibitors (NEPi), including sacubitril/valsartan, were developed to improve outcomes in heart failure and cardiovascular diseases by increasing natriuretic peptides, which promote vasodilation, diuresis, and natriuresis. Sa-

cubitril/valsartan, combining a neprilysin inhibitor and an angiotensin II receptor antagonist, was approved in 2015 for treating heart failure with reduced ejection fraction (HFrEF) and is recommended in American and European guidelines.[73] The PARADIGM-HF trial demonstrated consistent efficacy and safety of sacubitril/valsartan across different KDIGO kidney risk categories, with benefits in reducing both cardiovascular and renal events.[74] Moreover, a systematic review and meta-analysis examined the renal safety of NEPi, such as sacubitril/valsartan, compared to ACEi or ARBs; Sacubitril/valsartan or omapatrilat treatment was associated with a modestly reduced risk of renal events overall (OR 0.82 [0.7-0.97]) compared to ACEi or ARB therapy alone. Additionally, there was a lower incidence of severe acute renal events (OR 0.8 [0.69-0.93]) and a smaller decline in estimated glomerular filtration rate (eGFR) (mean difference -0.58 mL/min [-0.83 to -0.33 mL/min]). Furthermore, no significant differences were found in the rates of hyperkalemia. Despite indications of potential renal benefits, sacubitril/valsartan remains unused due to safety apprehensions. These findings highlight the importance of increasing its use and conducting further research on its long-term effects on CKD progression.[75]

MRA: Inflammation and fibrosis as potential targets of a therapeutic approach in CKD

The interplay between aldosterone, AT1 and AT2 and FGF23 acquires greater relevance if we consider that the overactivation of MR is a key event for chronic inflammation.[76] Increased aldosterone levels occur in presence of HF, regardless of ACE or ARB treatment. These high aldosterone levels correlate with a raised risk for metabolic syndrome, CV events and all-cause mortality. The mechanisms underlying this fearsome association encompass genomic and non-genomic effect. In the kidney, aldosterone stimulates the transcription of the serum glucocorticoid kinase (Sgk1). The Sgk1 inhibits the function of Nedd4-2 which in turn degrades ENaC channels in the proteasomes. Hence, the expression of ENaC on tubular cells membrane is increased in presence of aldosterone, leading to sodium reabsorption and excretion of potassium. Aldosterone plays a pivotal role in the collagen synthesis in myocardial arteries and continuous exposition to aldosterone leads to vascular inflammation with increased expression of cyclooxygenase-2 (COX-2), macrophage chemoattractant protein-1 (MCP-1), osteopontin and protein plasminogen activator inhibitor-1 (PAI-1).[77, 78] Moreover, markers of collagen turnover such as procollagen type III amino-terminal peptide (PIIINP) which increases in presence of aldosterone, has been associated with cardiac fibrosis and mortality. The pharmacological blockade of MR partially reverted matrix imbalances and thus, is able to reduce CV events with a magnitude that depends on the selectivity and efficacy of receptor antagonism.[79] Intriguingly, the MR function also depends on its localization, being this receptor expressed in cardiomyocyte, endothelial cells, vascular smooth cells muscle cells, macrophage and fibroblasts. In cardiomyocytes MR overexpression alters the duration of the action potential (mainly because of the activation of L-type calcium current) with increased incidence of arrythmias. In endothelial cells, high MR leads to fibrosis and increased cell to cell adhesion. In macrophages and fibroblast, MR activation basically leads to pro-inflammatory and pro-fibrotic pathways.[80]

FGF23 can contribute to these complex mechanisms by altering inflammatory cytokines expression, thereby forming a vicious cycle that, once activated, results in the uncontrolled production of both factors.[81]

Despite the solid body of evidence in HFrEF, data from clinical trials to prove the efficacy of steroidal MRAs in slowing the progression of CKD were sparse. The efficacy and safety of spironolactone and/or eplerenone when added to background therapy with an angiotensin-converting-enzyme-inhibitor or an angiotensin-receptor-blocker was explored in a 2020 Cochrane meta-analysis of 44 trials involving a total of 5,745 patients with albuminuria and CKD.[82] Compared with placebo or standard-of-care treatment, add-on administration of steroidal MRAs was associated with potential benefits on intermediate endpoints of cardiorenal diseases, such as albuminuria, eGFR slope, and clinic systolic blood

pressure. However, these beneficial effects were accompanied by a 2.17-fold increase in the risk of hyperkalemia, a 2.04-fold higher risk of acute kidney injury (AKI), and a 5.14-fold higher incidence of gynecomastia. Furthermore, none of these trials was adequately powered to detect benefits on clinical outcomes, such as kidney failure, major adverse cardiovascular events, or all-cause death.

Achieving the beneficial effects of MR blockade and avoiding the above-mentioned serious side effects, at the same time, is the aim of the new non-steroidal MRA. Finerenone represents a promising example of this drug class. Finerenone exerts a new type of MR blockade compared to steroidal MRA, *i.e.* it induces a conformational change in the MR structure. This aspect is crucial in the mechanism of action and nephroprotection, since it is associated with the recruitment of cofactors and the consequent repression of genes specifically involved in fibrosis and inflammation.[83] Two other major characteristics confer an advantage and prompt the use of finerenone: the lower half-life (2-3 hours) compared to eplerenone (4-6 hours) and spironolactone (>20 hours) and the high selectivity which, considering together, they explain the lower incidence of side effects such as hyperkalemia and gynecomastia. The development program of finerenone is still ongoing, with new studies aimed at demonstrating its efficacy in type 1 diabetes, non-diabetic CKD patients and CKD in children. However, two large phase 3 randomized studies, the FIDELIO and FIGARO have already shown that finerenone reduces the risk for CKD progression by 23% and the risk of fatal and non-fatal cardiovascular events by 14 to 22% in patients with type 2 diabetes and albuminuric CKD.[84, 85] Cardiorenal protection in these studies was associated with a significant

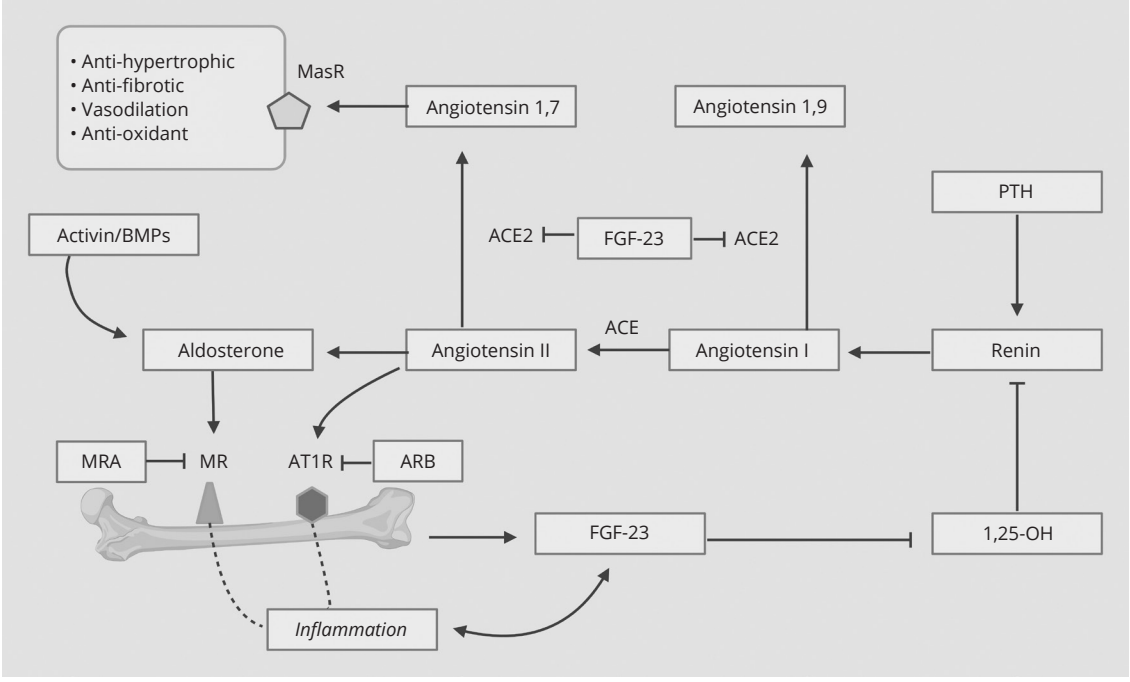

Figure 1.—The interplay among mineral bone disorders and RAAS. The figure illustrates the complex regulatory network that determines the interaction between RAA system and the bone. Activin/BMP system increases aldosterone production induced by Ang II. The receptors for angiotensin (AT1R) and aldosterone (MR) are expressed in the bone, which is the main site of FGF23 production. Angiotensin 1-7 and MasR are involved in counteracting the effects of the traditional RAA pathway, offering protective roles in vascular and renal health.
ACE: angiotensin converting enzyme; ACE-2: angiotensin converting enzyme 2; ARB: angiotensin receptor blocker; ATR: angiotensin receptor; BMP: bone morphogenic protein; CKD-MBD: chronic kidney disease - mineral and bone disorder; FGF-23: fibroblast growth factor-23; MR: mineralcorticoid receptor; MRA: mineralcorticoid receptor antagonist; PTH: parathormone; RAAS: renin-angiotensin-aldosterone system; 1,25-OH: 1,25-dihydroxyvitamin D.

reduction in albuminuria and was independent from blood pressure reduction.

There is sufficient evidence to suggest that treatment with MRA including finerenone might reduce albuminuria, the progression of chronic kidney disease and eliminate the renal inflammation by reducing the expression of pro-inflammatory cytokines, such as MCP-1, TNF-α and Matrix metalloproteinase-12 (MMP-12).[83]

The interaction between FGF23 and RAAS does not represent the only potential link between mediators of mineral metabolism RAAS and ultimately CKD progression (Figure 1). PTH increases the secretion of aldosterone from the adrenals directly as well as indirectly by activating the RAAS.[86] Indeed, preclinical studies demonstrate in kidney, skeleton, vasculature and heart during CKD an upgrade of signaling of activins, inhibins and bone morphogenetic proteins (BMPs): these molecules are dimeric polypeptides members of the TGF-b superfamily. This supports the hypothesis that these molecules produced in the kidney during kidney disease, in addition to promoting the progression of kidney damage, deranges other organs' homoeostasis independently of changes in PTH and FGF23 and participating in CKD-MBD.[56]

Conclusions

Despite significant advances in treatment options that slow CKD progression the target annual decline rate has not been reached as well as the pathogenesis of aldosterone breakthrough is still far from being defined.

All these claims to carry out new studies able to define the interrelationship of FGF23, PTH, Activins, aldosterone and RAAS blockade and the response to a treatment with a steroidal vs nonsteroidal MRA. Above all these features underline the hypothesis that MBD and RAAS are not planets belonging to different galaxies but represent different but strictly related pathways of the same process involved in CKD progression.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Giuseppe Cianciolo, Michele Provenzano: conceptualization; supervision; writing- original draft preparation; writing – review and editing; visualization. Lilio Hu, Simona Barbuto: writing – original draft preparation; writing – review and editing; visualization. Maria J. Soler, Paola Ciceri, Mario Cozzolino: writing – review and editing; visualization. Gaetano La Manna: supervision; writing – review and editing; visualization. All authors read and approved the final version of the manuscript.

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