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Cardiac hypertrophy in chronic kidney disease—role of Aldosterone and FGF23

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Abstract

Cardiac hypertrophy is a life-threatening disorder and is frequently observed in patients with chronic kidney disease (CKD). Much attention has been focused on the derangement in hormonal factors, including aldosterone and FGF23, as novel causes of cardiac hypertrophy in CKD. Plasma aldosterone concentrations are elevated as renal function declines. Although aldosterone antagonists are available for the treatment of hypertension with cardiac hypertrophy, concern remains regarding the possible occurrence of serious hyperkalemia. Alternatively, certain types of calcium channel blockers suppress aldosterone synthesis or exert blocking action for mineralocorticoid receptors and could halt the progression of cardiac dysfunction. Recently, FGF23 is shown to be elevated as CKD progresses and may be responsible for the development of cardiac hypertrophy and heart failure. Furthermore, FGF23 not only inhibits the renal expression of angiotensin converting enzyme 2 but also enhances renin gene transcription, both of which could accelerate renin-angiotensin-aldosterone system. Although the increase in serum phosphate concentrations is a pivotal stimulus for FGF23 production, recent studies suggest that reduced iron status and elevated aldosterone levels, frequently seen in patients with CKD or on dialysis, might also contribute to the elevation in serum FGF23 levels. Conversely, phosphate binders and appropriate iron status could reduce serum FGF23, potentially leading to the alleviation of cardiac hypertrophy and heart failure. In conclusion, novel therapeutic strategies associated with aldosterone and FGF23 may confer a benefit in the management of cardiac disorders in CKD.

Keywords: Aldosterone, FGF23, Cardiac hypertrophy, Phosphate, Iron, Ca channel blockers, Mineralocorticoid receptor antagonists, Heart failure, Chronic kidney disease

Background

Chronic kidney disease (CKD) is a life-threatening disorder and relentlessly progresses to end-stage kidney disease requiring renal replacement therapy. A growing body of evidence has been accumulated that CKD is closely associated with increased risk of cardiovascular events and death. Go et al. [1] demonstrated that the event rate inversely parallels the level of renal function. Likewise, cardiovascular events are associated with the reduction in glomerular filtration rate (GFR) among Japanese population [2, 3]. Cardiovascular disease observed in CKD includes a variety of disorders such as heart failure and cardiac hypertrophy. Since cardiac hypertrophy per se is more prevalent as renal function deteriorates and reflects an ominous outcome with increased mortality [4, 5], the alleviation of this disorder would offer improved survival to CKD patients.

Although hemodynamic derangement such as systemic hypertension and volume overload plays a major role in the development of cardiac hypertrophy, several lines of recent studies indicate that humoral factors also contribute to the development of cardiac hypertrophy. For example, angiotensin II is a well-known factor that exerts direct hypertrophic action on cardiomyocytes [6, 7]. Further evidence has accrued that aldosterone, a traditional hormone regulating serum electrolyte balance, not only induces renal glomerular hypertension [8] but also causes cardiac hypertrophy [9, 10] and heart failure [11]. Because such humoral factors are often elevated in CKD [12–15], the strategy to counter the action of these factors would improve various perturbed conditions in CKD and is currently proposed as a milestone treatment of CKD, particularly with the use of renin-angiotensin system (RAS) inhibitors [10, 11, 16, 17].

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It is well recognized that CKD is accompanied by a variety of disturbance of the internal milieu, including electrolyte disorders. Despite impaired ability of renal excretory function, serum phosphate levels remain relatively unchanged until GFR falls below half of the normal level. Recent studies disclose that fibroblast growth factor 23 (FGF23) contributes importantly to the regulation of the serum phosphate concentration by inhibiting the phosphate reabsorption in the proximal tubule, which mitigates the tendency toward phosphate retention in CKD [18, 19]. Although this mechanism teleologically serves to act as an adaptive regulatory factor to maintain serum phosphate levels constant, further deterioration of CKD causes the elevation in serum phosphate concentrations, which hence would stimulate FGF23 production. Furthermore, of importance is the finding that elevated serum FGF23 concentrations are associated with the development of cardiac disorders [20–23]. Thus, apparently homeostatic mechanism for phosphate metabolism may act to aggravate cardiac disease, leading to cardiac hypertrophy and heart failure.

In this review, we survey the role of aldosterone in the development of cardiac hypertrophy in CKD and evaluate the therapeutic strategy for aldosterone blockade. Furthermore, recent findings regarding the effect of FGF23 on cardiac hypertrophy as well as the modulatory factors or therapeutic tools affecting FGF23 production are also discussed.

Aldosterone in CKD

Canonical concept of aldosterone is typically referred to as the hormone regulating electrolyte metabolism in the epithelial cell, i.e., sodium and potassium balance in renal tubular cells, intestinal epithelial cells, and sweat glands. Among these, renal distal and collecting tubules are the major target sites of action of aldosterone, where aldosterone facilitates sodium reabsorption through epithelial sodium channels (ENaC) and concomitantly potassium excretion mainly through ROMK channels [24]. Furthermore, aldosterone upregulates Na/K/ATPase that extrudes sodium from the cell to interstitial spaces as well as augments the uptake of potassium into the cell [25]. The overall action of aldosterone comprises volume expansion, hypertension, and the decrease in serum potassium levels, as are evident in primary aldosteronism.

Plasma aldosterone levels are regulated by a couple of factors (Fig. 1). Angiotensin II and ACTH represent major regulatory hormones stimulating aldosterone synthesis. Furthermore, high serum potassium levels induce aldosterone release from adrenal cortical gland. In addition, previous studies demonstrated that plasma aldosterone concentrations were elevated in CKD [15, 26–30] and were correlated inversely with renal function [15] (Fig. 1). Although high potassium obviously constitutes a stimulus for aldosterone release in CKD, reduced aldosterone excretion is reported as a possible cause of elevated plasma aldosterone concentrations [31]. Alternatively, Wesson and Simoni [27] showed that acid retention during kidney failure induced aldosterone production and elevated plasma aldosterone concentrations. Furthermore, Hosoya et al. [15] have recently demonstrated that the expression of the aldosterone-producing enzyme CYP11B2 in the adipose tissue of 5/6-nephrectomized rats is upregulated, leading to increased tissue aldosterone content. Finally, aldosterone breakthrough phenomenon (i.e., an elevation in plasma aldosterone levels 3–6 months after the administration of RAS inhibitors) could be a possible mechanism for aldosterone dysregulation [32, 33]. Taken together, these mechanisms may act in concert to enhance aldosterone activity in CKD.

The kidney plays an important role in potassium homeostasis. In subjects with intact kidney function, approximately 90% of potassium is excreted from the kidney where aldosterone contributes importantly to potassium excretion, and only 10% of potassium is secreted from the intestine. In patients with end-stage kidney disease, including dialysis patients, however, potassium secretion from the large intestine is considerably increased [29, 34, 35], in which $K_{Ca}1.1$ (BK) channels are largely involved [36]. Whereas aldosterone is shown to enhance the colonic BK channel activity [37, 38] and contributes at least partly to the increased colonic potassium excretion [39], there are also reported several studies showing a modest role of aldosterone in colonic potassium secretion in both predialysis [29, 40] and dialysis CKD patients [35]. It requires further discussion whether aldosterone blockade causes perilous levels of hyperkalemia in dialysis patients with end-stage kidney disease (see below).

Non-epithelial action of aldosterone

In addition to conventional action in epithelial cells, aldosterone is demonstrated to exert non-epithelial action in various organs. In the study evaluating the role of aldosterone in patients with heart failure, treatment with a mineralocorticoid receptor blocker (spironolactone) on top of conventional therapies (i.e., ACE inhibitors plus diuretics) conferred a profound benefit in terms of survival rate [11]. Since this clinical trial (i.e., RALES), a novel idea has emerged that aldosterone constitutes a critical determinant of cardiac function in patients with heart failure. Similarly, Zannad et al. [41] showed that a more selective aldosterone blocker, eplerenone, reduced the risk of death and hospitalization among patients with systolic heart failure and mild symptoms. It has also been demonstrated that aldosterone causes detrimental effects on vascular tension (enhanced vascular tone) [42] and glucose metabolism (insulin resistance) [15], both of which could influence mortality and morbidity.

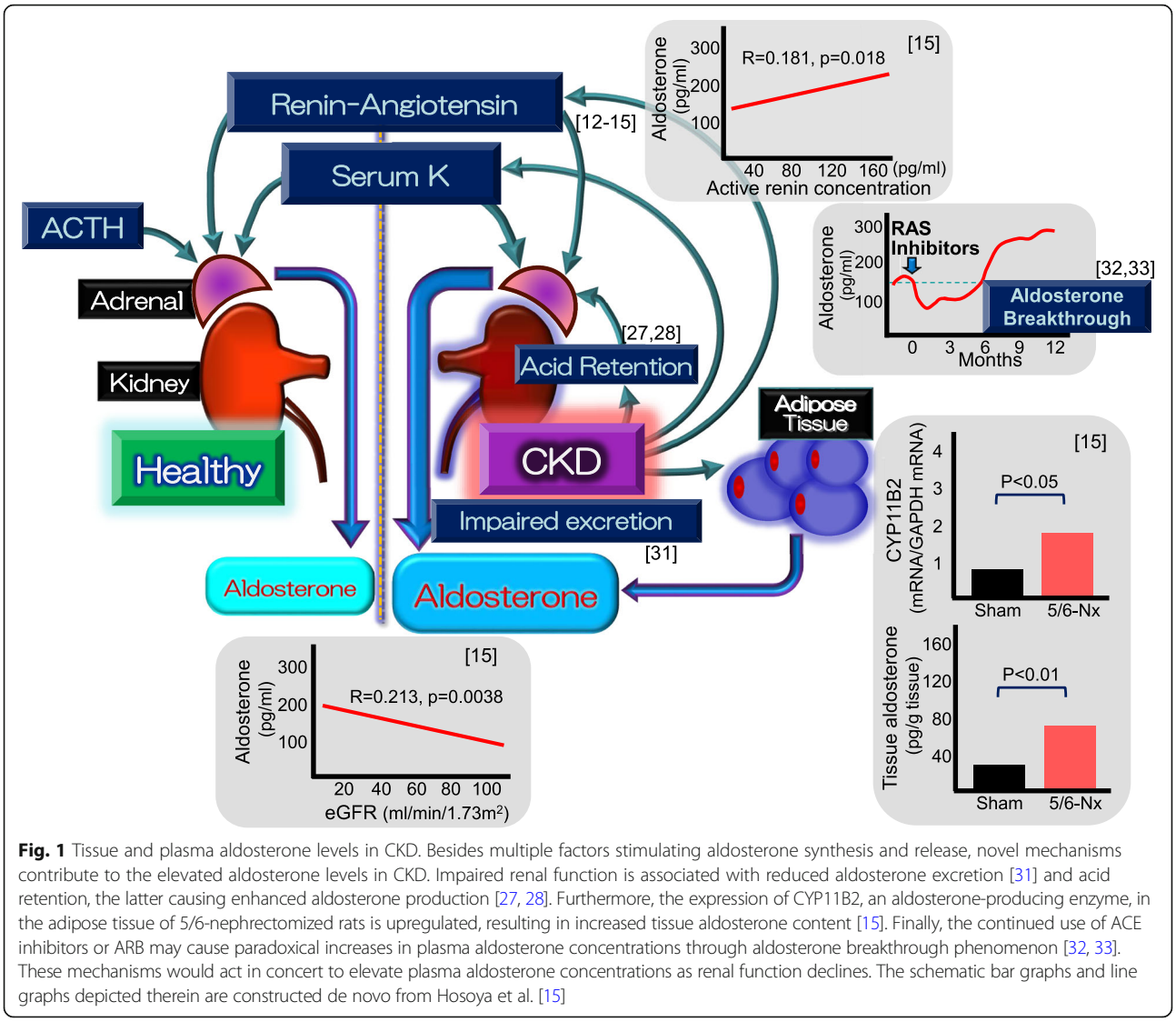

Fig. 1 Tissue and plasma aldosterone levels in CKD. Besides multiple factors stimulating aldosterone synthesis and release, novel mechanisms contribute to the elevated aldosterone levels in CKD. Impaired renal function is associated with reduced aldosterone excretion [31] and acid retention, the latter causing enhanced aldosterone production [27, 28]. Furthermore, the expression of CYP11B2, an aldosterone-producing enzyme, in the adipose tissue of 5/6-nephrectomized rats is upregulated, resulting in increased tissue aldosterone content [15]. Finally, the continued use of ACE inhibitors or ARB may cause paradoxical increases in plasma aldosterone concentrations through aldosterone breakthrough phenomenon [32, 33]. These mechanisms would act in concert to elevate plasma aldosterone concentrations as renal function declines. The schematic bar graphs and line graphs depicted therein are constructed de novo from Hosoya et al. [15]

Besides the critical role of aldosterone in survival rates in heart failure [11, 41], accumulating evidence indicates that aldosterone is responsible for the development of cardiac hypertrophy and impaired cardiac function. In primary aldosteronism in which overproduction of aldosterone causes hypertension, left ventricular (LV) hypertrophy can be induced independently of systemic hypertension [43, 44]. Furthermore, in patients with CKD, plasma aldosterone concentrations are inversely associated with GFR [15, 30] and parallel LV mass index [30]. Alternatively, aldosterone blockade with spironolactone elicited a regression of LV hypertrophy despite no changes in systemic blood pressure in diabetic patients with microalbuminuria [10] (Table 1). Furthermore, spironolactone treatment significantly ameliorated LV mass index and/or cardiac function not only in patients with early stage CKD [45, 46] but also in patients with advanced CKD on hemodialysis [47–49] or peritoneal dialysis [50–52]. More importantly, Matsumoto et al. [53] elegantly demonstrated that 3-year treatment with spironolactone reduced the death rate from cardiovascular or cerebrovascular events in patients on hemodialysis in Dialysis Outcomes Heart Failure Aldactone Study (DOHAS). In concert, these observations suggest that aldosterone is responsible substantially for the development of cardiac hypertrophy and remodeling in humans.

Although aldosterone has a great impact on cardiovascular organs, multiple signal transduction systems appear to be involved in the non-epithelial action of aldosterone. Several lines of experimental studies show that aldosterone promotes the signal transduction of ERK pathways [54, 55] and generates reactive oxygen species [56] and inflammation [57], all of which cause cardiac hypertrophy and remodeling. Very recently, it has been demonstrated that aldosterone upregulates TNF receptor-associated factor 3 interacting protein 2

Table 1 Aldosterone blockers for LV hypertrophy in CKD

	Authors	Study duration	LV mass index	LV function	Hyperkalemia vs placebo	Ref
CKD						
DM nephropathy	Sato A. et al.	24 weeks	Decreased		(No change)	[10]
Stage 2~3 CKD	Edwards NC et al.	40 weeks	Decreased	Improved	No difference	[45, 46]
Hemodialysis						
	Feniman-De-Stefano GM et al.	6 months	Decreased	No change	No difference	[47]
	Taheri S et al.	6 months	Decreased	Improved	No difference	[48]
	Lin C. et al.	2 years	Decreased	Improved	No difference	[49]
	Matsumoto Y et al.	3 years	Reduced death from cardiovascular events		3 of 157 patients discontinued	[53]
Peritoneal dialysis						
	Ito Y. et al.	2 years	Decreased	Improved	No difference	[50]
	Taheri S. et al.	6 months		Improved	No difference	[51]
	Hausmann MJ et al.	10 months		Improved	(No change)	[52]

(TRAF3IP2), which serves as an upstream regulator of multiple signaling components, including I kappa B kinase, JNK and c-Jun, and then stimulates the production of IL-18, IL-6, and CTGF [58, 59]. These results hence indicate a pivotal role of TRAF3IP2 and the multiple subordinate signal transduction pathways described above in mediating the aldosterone-induced adverse cardiac effects. Of interest, the mineralocorticoid receptor pathway is also stimulated by Rac1 activation through salt loading [60] and obesity [61] as a ligand-independent modulator without alterations in systemic aldosterone status. Furthermore, the Rac1-mediated activation of the mineralocorticoid receptor in the myocardium is responsible for the development of heart failure [62]. It follows therefore that mineralocorticoid receptor activation, whether a ligand-dependent or not, stimulates the downstream signaling pathways associated with growth and inflammation and induces cardiac hypertrophy and impaired contractility.

Aldosterone blockade in CKD

As indicated above, aldosterone blockade reduces cardiac hypertrophy and improves cardiac function in patients on hemodialysis [47–49] and peritoneal dialysis [50–52] (Table 1). Furthermore, DOHAS trial clearly demonstrates that aldosterone blockade by spironolactone prevents cardiovascular events and ameliorates the survival rate in hemodialysis patients [53]. Caveat is in order, however, because of the potential risk for hyperkalemia when the blockers are given to CKD patients. Thus, potassium secretion from the intestine is increased in patients with advanced CKD or on dialysis therapy [29, 34, 35], and mineralocorticoid receptor blockers are reported to suppress this mechanism [38]. Indeed, several studies have reported that the administration of spironolactone is associated with increased incidence of hyperkalemia in patients on maintenance hemodialysis therapy [63–65] although pronounced hyperkalemia (serum potassium ≥ 6 mEq/L) does not occur commonly [66]. Notably, there are also reported a substantial number of studies showing that spironolactone does not cause significantly higher levels of serum potassium in patients on hemodialysis [47–49] or peritoneal dialysis therapy [50, 51, 67, 68], when compared with placebo (Table 1). Taken together, the use of aldosterone blockers is teleologically reasonable in terms of cardiovascular protection, although the adverse effect of these blockers might hamper the wide-spread use of this type of agents in patients with CKD.

Alternatively, there exist several types of antihypertensive agents that act to inhibit aldosterone synthesis and/or release (Table 2) [69]. It is now well established that certain types of calcium channel blockers, including efonidipine [70], benidipine [71], azelnidipine [72], and cilnidipine [73], inhibit aldosterone synthesis in adrenocortical cells. Furthermore, clinical studies show that these agents decrease serum aldosterone levels in hypertensive patients [74–79]. Of interest, these calcium channel blockers are endowed with the ability to inhibit not only L-type but also T-type (efonidipine, benidipine, azelnidipine) or N-type calcium channels (benidipine, cilnidipine), whereas conventional calcium channel blockers such as nifedipine and amlodipine exert inhibitory action solely on L-type calcium channels [80–82]. Additionally, several calcium channel blockers, including nifedipine and benidipine, are shown to compete with aldosterone for mineralocorticoid receptor binding and block aldosterone activity [83, 84] (Table 2). Thus, divergent inhibitory action on calcium channel subtypes (i.e., L-, T-, and N-type calcium channels) and

Table 2 Calcium channel blockers affecting aldosterone synthesis

Ca channel blockers	Inhibition of Ca channel subtypes			Inhibition of aldosterone production		Mineralocorticoid receptor blockade
	L-type	T-type	N-type	Adrenal cells	Human plasma concentrations	
Nifedipine	+					+ [83]
Amlodipine	+					
Efonidipine	+	+		+ [70]	+ [74, 75]	
Nilvadipine	+	+				
Azelnidipine	+	+		+ [72]	+ [77]	
Cilnidipine	+		+	+ [73]	+ [78, 79]	
Benidipine	+	+	+	+ [71]	+ [76]	+ [84]

distinct antagonistic action on mineralocorticoid receptors inherent in certain calcium channel blockers could provide additive cardiovascular benefits in CKD patients. Indeed, in our preliminary study, we found that T-type calcium channel blockers (efonidipine, benidipine, azelnidipine) and nifedipine reduced LV mass index more markedly than other calcium channel blockers in hemodialysis patients (unpublished observation). This presumption, however, requires further investigations showing that these calcium channel blockers could contribute to the prevention of cardiac hypertrophy.

FGF23 and phosphate in CKD

FGF23 is identified as a glycoprotein hormone that has been discovered as a member of the FGF family [85]. The subsequent investigations have unveiled an important role of FGF23 in the homeostatic mechanism of serum phosphate levels [18, 19]. The conventional hypothesis, i.e., "trade-off theory" [86, 87], where secondary hyperparathyroidism is assumed to play a central role in phosphate metabolism in CKD, therefore, has been updated by the introduction of FGF23 to the concept of the phosphate metabolism in CKD.

Serum FGF23 levels have been shown to rise at early stages of CKD. Several studies demonstrate that serum FGF23 is elevated even prior to the stage when serum parathyroid hormone rises [19, 88]. Although the precise cellular mechanisms for the release and synthesis of FGF23 remain fully undetermined, the elevation in serum phosphate and parathyroid hormone constitute determinants that trigger the release of FGF23 from osteocytes and osteoblasts (Fig. 2). Because FGF23 is a potent phosphaturic hormone that inhibits phosphate reabsorption through Na/P cotransporter 2a/c in the proximal tubule [18, 86, 89], FGF23 would serve to mitigate hyperphosphatemia entailing impaired renal function. FGF23 also suppresses vitamin D activity by inhibiting renal 1α-hydroxylase (the enzyme that converts 25-hydroxyvitamin D3 to its active form) and stimulating 24-hydroxylase (the enzyme degrading to inactive form) [90], leading to the decrease in phosphate and calcium absorption from the intestine. Although FGF23 can inhibit parathyroid hormone production [88, 91], the effects of suppressed vitamin D activity along with decreased Ca levels would govern the serum parathyroid hormone level more robustly in CKD, which results in elevated parathyroid hormone levels characteristics of the hormonal profiles seen in CKD patients [92, 93].

FGF23 and sodium in CKD

In addition to the phosphaturic action in renal proximal tubules, FGF23 is found to exert sodium retaining action in distal tubular segments. Thus, Andrukhova et al. [94] have recently demonstrated that FGF23 upregulates the sodium chloride cotransporter (NCC) in distal tubules, which conceivably results in systemic volume expansion and hypertension (Fig. 2). This finding encompasses an important issue because FGF23 could cause the suppression of RAS due to systemic volume expansion and subsequently decrease plasma aldosterone levels [95]. In contrast, a positive correlation between FGF23 and aldosterone concentrations is also reported in patients with CKD and heart failure [96]. In this regard, CKD is demonstrated to be associated with decreased renal expression of Klotho [97, 98]. Since the action of FGF23 on NCC requires the integrity of the FGF receptor/Klotho complex [94], the ability of FGF23 to promote sodium retention and the subsequent development of hypertension may depend on intact FGF receptor/Klotho complex activity. Indeed, the observation that plasma aldosterone levels are elevated in advanced CKD [12–15, 26, 27, 29] suggests the diminished ability of elevated FGF23 to induce volume expansion, possibly due to reduced Klotho expression in the kidney.

FGF23 and RAS/aldosterone

Recent investigations reveal a cross talk between FGF23 and RAS/aldosterone [99] (Fig. 2). Dai et al. [100] demonstrated that FGF23 suppressed the renal expression of angiotensin converting enzyme 2 (ACE2), the enzyme mediating the conversion mainly from angiotensin II to angiotensin-(1-7), in FGF23-transgenic mice. The

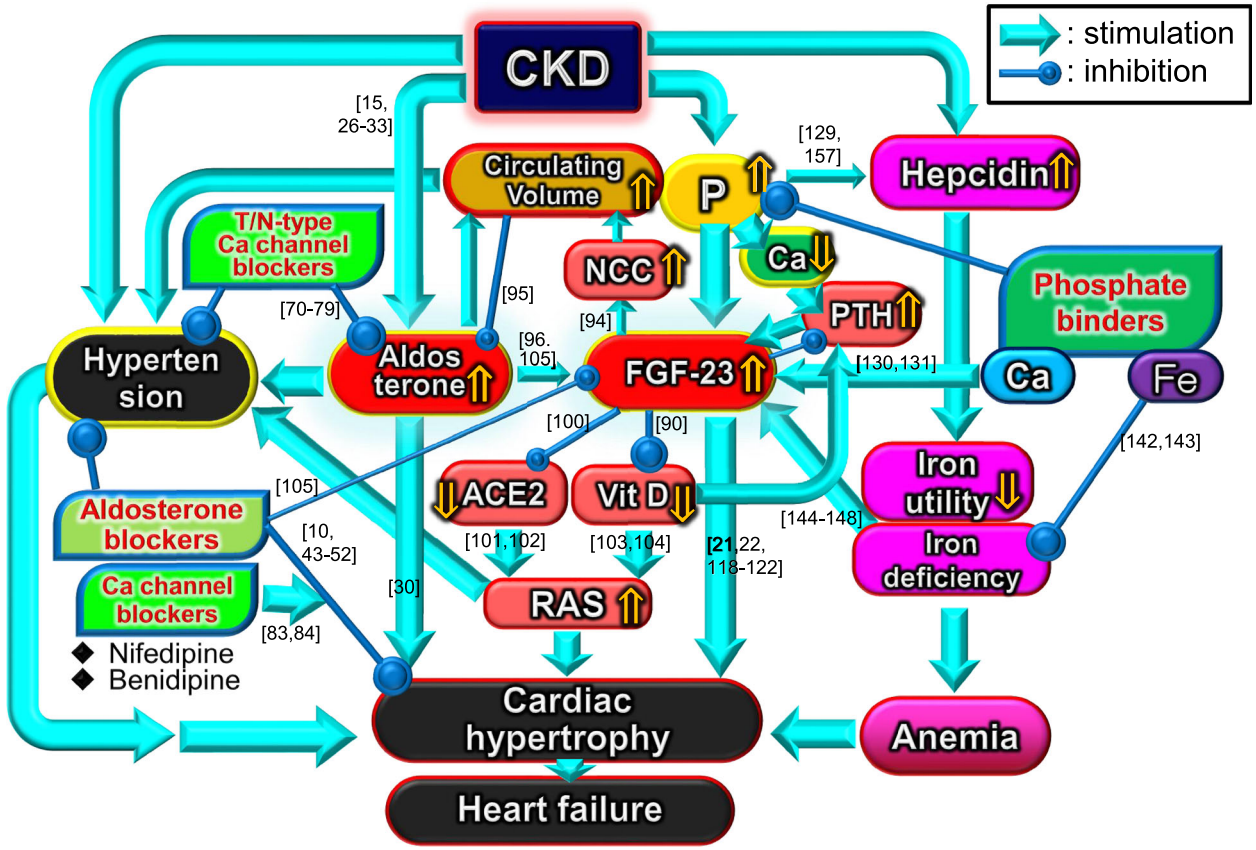

Fig. 2 Schematic diagram illustrating the possible relationship of the hormonal factors associated with cardiac disorders in CKD. In CKD, both aldosterone and FGF23 are elevated, which directly and/or indirectly causes cardiac hypertrophy and heart failure. There is reported substantial interaction between aldosterone and FGF23, directly from aldosterone to FGF23 and indirectly from FGF23 to aldosterone through circulating volume status. Additionally, elevated FGF23 inhibits vitamin D activity and angiotensin converting enzyme 2 (ACE2) expression, both of which could result in augmentation in renin-angiotensin-aldosterone system. Aldosterone blockade by mineralocorticoid receptor antagonists and T-/N-type Ca channel blockers could mitigate cardiac hypertrophy. Phosphate binders not containing Ca reduce FGF23 and could potentially ameliorate cardiac hypertrophy, while those containing iron exert FGF23-lowering action not only through reducing serum phosphate but also through iron supplementation. NCC, sodium chloride cotransporter; ACE2, angiotensin converting enzyme 2; RAS, renin-angiotensin system; PTH, parathyroid hormone. The numbers in brackets denote the references cited in the text

suppression of ACE2 activity results in the decrease in vasodilatory angiotensin-(1-7) and the increase in angiotensin II [101, 102]. It is inferred therefore that in CKD, where plasma FGF23 is elevated, altered balance between angiotensin II and angiotensin-(1-7) might play a part in hypertension and volume retention. Furthermore, accumulating evidence indicates that vitamin D inhibits RAS by downregulating renin gene transcription [99, 103, 104]. Because FGF23 suppresses vitamin D activity, elevated plasma FGF23 would augment RAS and possibly aldosterone as well and may play a role in the development of hypertension in CKD.

Finally, the interaction between FGF23 and aldosterone merits comment. Imazu et al. [96] showed that serum FGF23 levels correlated with plasma aldosterone concentrations in patients with CKD and heart failure. An in vitro study also demonstrates that FGF23 transcription is upregulated by aldosterone and is inhibited by an aldosterone receptor blocker (eplerenone) in cultured osteoblasts [105]. Although clinical evidence endorsing a causative role of aldosterone in FGF23 production remains insufficient, these findings are consistent with the notion that aldosterone contributes to the enhanced FGF23 production in CKD (Fig. 2).

FGF23 and cardiac hypertrophy

Cardiac hypertrophy is a critical complication that is frequently observed in CKD [106, 107]. Cardiac hypertrophy develops beginning at early stages of CKD and is quite common in patients on dialysis therapy. In addition to the traditional determinants causing cardiac hypertrophy, including hypertension, renin-angiotensin system [6, 7], and chronic anemia [108], aldosterone is also established as a crucial factor for cardiac hypertrophy [9, 10, 15, 30,

43]. Furthermore, parathyroid hormone is suggested as a cause of cardiac hypertrophy in dialysis patients [109, 110], although contradictory results are also reported [111, 112]. Of interest, mineralocorticoid receptor blockade reduces serum parathyroid hormone levels in normal subjects as well as in patients with CKD and heart failure, suggesting that aldosterone stimulates parathyroid hormone production [113, 114]. Alternatively, parathyroid hormone enhances the aldosterone secretion from adrenal cortex [115, 116]. Clinical implications of these interactions in the development of cardiac hypertrophy, however, remain undetermined [117].

More recently, much attention has been focused on the role of FGF23 since this substance not only participates in the phosphate homeostasis but also induces cardiac hypertrophy (Table 3) [21, 22, 118–122]. Thus, Gutierrez et al. [21] discovered that there existed a close relationship between serum FGF23 levels and LV mass index in patients with CKD. Faul et al. [22] also demonstrated that LV mass index was increased as serum FGF23 levels were elevated. This relationship was also observed in patients on maintenance hemodialysis. Finally, intravenous injection of FGF23 caused cardiac hypertrophy in mice, and the administration of an FGF receptor antagonist (PD173074) prevented the development of the CKD (i.e., 5/6 nephrectomy)-induced cardiac hypertrophy. Of importance, elevated serum FGF23 levels are causally linked to reduced ejection fraction [22]. Collectively, these observations provide conclusive evidence for the role of FGF23 in the development of cardiac disorders in CKD.

Although a growing body of evidence has been accumulated regarding the role of FGF23 in cardiac hypertrophy in CKD, the mechanism responsible for the cardiac disorder remains undetermined fully. In experimental models of mice, Faul et al. [22] demonstrated that the FGF23-induced cardiac hypertrophy was abrogated by a phospholipase Cγ inhibitor (U73122) and a calcineurin inhibitor (cyclosporine A), but not by a MAP kinase inhibitor (PD98059), a PI3 kinase inhibitor (wartmannin), or an Akt inhibitor (A6730). Furthermore, pan FGF receptor blockade by PD173074 reduced LV mass and the cardiac expression of genes associated with LV hypertrophy [123], and the receptor involved was identified as FGF receptor 4 [124]. These findings lend support to the premise that FGF23-induced cardiac hypertrophy is mediated by the FGF receptor 4/PLCγ/calcineurin pathway.

Role of phosphate binders in FGF23 levels and iron metabolism

Great progress in the therapeutic modalities for phosphate binders offers more favorable management of serum phosphate levels in CKD. Following the established use of Ca carbonate, new (i.e., second generation) phosphate binders, including sevelamer, bixalomer, and lanthanum carbonate,

Table 3 FGF23 and cardiac hypertrophy in CKD

Authors	*n*	Effects of FGF23 on cardiac hypertrophy	Ref.
Humans			
Gutierrez OM et al.	162 CKD	Incidence of LVH (%), FGF23 < 75 RU/ml; 7%, 75–150 RU/ml, 21%, > 150 RU/ml; 25%	[21]
Faul C et al.	3070 CKD	Incidence of LVH (eccentric+concentric)%, FGF23 quarfile 1; 38%, quarfile 2; 45%, quartile 3; 54%, quarfile 4; 70%	[22]
Hsu HJ et al.	124 hemodialysis	Serum FGF23 level is independently associated with LVH in hemodialysis patients	[118]
Seifert Me et al.	31 CKD stage 3	The change in FGF23/klotho ratio was strongly correlated with changes in LV mass index.	[119]
Sarmento-Dias M et al.	48 peritoneal dialysis	In multivariate adjusted analysis, FGF23was associated with LVMI ($\beta = 0.298$, $p = 0.041$),	[120]
Javanovich A et al.	2255 elderly CKD	Higher FGF23 concentrations were associated with greater LVM in adjusted analyses ($\beta = 6.71$ [95% CI 4.35–9.01] g per doubling of FGF23).	[121]
Tanaka S. et al	903 CKD stage 1 to 5	The correlation between FGF23 and LVMI was significant among those with CKD stage G1/G2, G3a, and G4.	[122]
Chue CD. et al	120 CKD stage 3	Sevelamer carbonate reduced FGF23 but failed to improve LV mass	[134]
Animals			
Maizel J et al.	CKD mice	Sevelamer reduced serum phosphate and LV hypertrophy but not FGF23.	[135]
Yamazaki-Nakazawa A et al.	CKD rats	Lanthanum carbonate reduced LV weight but failed to decrease FGF23 levels.	[136]

have come into common use. Because of the physiological interaction between serum phosphate and FGF23, it is judiciously anticipated that phosphate binders should reduce serum FGF23 levels [125–129]. In this regard, Ca load is reported to be associated with an elevation in serum FGF23 levels [130, 131] (Fig. 2). Furthermore, a cross-sectional study shows that FGF23 levels correlate with serum Ca ion concentrations and Ca-phosphate product [132]. Thus, phosphate binders containing Ca (e.g., Ca carbonate) may have less ameliorating impact on serum FGF23 levels than those without Ca (e.g., sevelamer, lanthanum) in both pre-dialysis [133] and dialysis patients [125, 128, 129].

Although FGF23 constitutes an important determinant inducing cardiac hypertrophy, whether the improvement in serum FGF23 levels by phosphate binders exerts beneficial action on cardiac hypertrophy is a matter of controversy (Table 3). Thus, it has been reported that 40-week treatment with sevelamer decreases serum FGF23 levels but fails to reduce LV mass in patients with stage 3 CKD, though the inability to ameliorate LV mass might be attributable to the insufficient treatment period [134]. Furthermore, sevelamer and lanthanum are shown to reduce serum phosphate concentrations and ameliorate LV hypertrophy without changes in FGF23 levels in experimental animals [135, 136]. Of interest, a strong association between serum phosphate concentrations and LV mass is demonstrated in humans [137, 138] and animals [139], and hyperphosphatemia per se could be a potential risk factor causing cardiac hypertrophy [140, 141]. Accordingly, the ability of phosphate binders to alleviate cardiac hypertrophy may vary, depending on the responsiveness of serum FGF23 and/or phosphate to these drugs. Further investigations are required to clarify this important issue.

Recently, iron-containing phosphate binders, including ferric citrate hydrate and sucroferric oxyhydroxide, have been developed and are actually available in clinical practice [142, 143]. Because of the nature of iron loss during hemodialysis sessions, the use of this type of phosphate binders appears reasonable in such condition since iron is dissociated from the binders and then absorbed in part from the intestine. Of note, iron deficiency and the subsequent anemia are associated with the elevation in plasma FGF23 concentrations [95, 144–147] and the upregulation of bone FGF23 mRNA expression (Table 4) [147, 148]. An in vitro study also shows that osteocytes in the medium containing low iron produce greater FGF23 mRNA expression [149]. Conversely, oral [146, 150, 151], but not intravenous [152, 153], iron supplementation is associated with a decrease in serum FGF23 levels. Additionally, switching from sevelamer to ferric citrate hydrate has recently been shown to replenish iron status and reduce

Table 4 Iron status and FGF23

Authors	Subjects/animals, *n*	Iron deficiency and FGF23	Ref.
Humans			
Bozentowics-Wikarek M et al.	3780 elderly	Low iron levels are associated with increased FGF23 levels. FGF23 levels were nearly linearly increased by 0.285 pg/mL for each unit of serum iron decrease in patients with serum iron levels < 59 ng/mL,	[144]
Lewerin C et al.	1010 elderly	FGF 47.4 μmol/L (transferrin saturation (TS) < 15%) vs 41.9 μmol/L (TS > 15%)	[145]
Braithwaite V. et al.	79 children non-CKD	Iron status is a negative predictor of plasma FGF23 concentration. Improvements in iron status following iron supplementation are associated with a significant decrease in FGF23 concentration.	[146]
Deger SM et al.	73 hemodialysis	There was a negative relationship between iron administration and serum iFGF23 level in a dialysis population	[150]
Yamashita K et al.	31 hemodialysis	Serum FGF23 was reduced from 1820 pg/mL (342-4370) to 1240 pg/mL (214-2840) after 3-month treatment with sodium ferrous citrate.	[151]
Takeda Y, et al	27 hemodialysis	Intravenous saccharated ferric oxide induces further increase in FGF23 levels.	[152]
Iguchi A et al	124 hemodialysis	Serum FGF23 level decreased from 2000 pg/mL (1300-3471.4) to 1771.4 pg/mL (1142.9-2342.9) after switching from sevelamer to ferric citrate hydrate.	[154]
Animals			
David V et al	Mice	Three-week low iron diet intake resulted in significantly increased levels of bone FGF23 mRNA. Functional iron deficiency with hepcidin injection caused increased bone expression of FGF23 mRNA.	[147]
Hanudel MR et al	Adenin-induced CKD mice	Eight-week adenine-containing and low iron diet intake increased the bone FGF23 mRNA levels.	[148]
Farrow EG et al.	Mice	Mice receiving low-iron diet had significantly elevated bone Fgf23 mRNA.	[149]
Gravesen E et al.	Non-iron depleted uremic rats	Intravenous iron isomaltoside and ferric carboxymaltose had no effect on plasma levels of FGF23 and phosphate.	[153]

circulating FGF23 levels independently of serum phosphate concentrations in hemodialysis patients [154]. In concert, an appropriate level of iron status is required to suppress serum FGF23 levels and potentially to prevent the development of cardiac hypertrophy.

In this regard, hepcidin, a regulatory molecule that inhibits iron absorption in the duodenum and iron recruitment from the liver and the reticuloendothelial system, is elevated in CKD [155, 156]. Furthermore, serum hepcidin levels are tightly associated with serum phosphate concentrations [157], and the reduction in serum phosphate by lanthanum is causally correlated with the decrement in serum hepcidin levels [129]. These observations therefore suggest complex interaction between phosphate-FGF23 pathways and iron metabolism (Fig. 2).

Conclusions

Cardiac hypertrophy is a serious complication observed frequently in patients with CKD. Among multiple factors involved in cardiac disease, humoral factors, including aldosterone and FGF23, are gaining much attention as critical components responsible substantially for the development of cardiac hypertrophy and heart failure that lead to increased morbidity and mortality. Recent progresses in the therapeutic strategies using novel tools facilitate the management of CKD. Novel approaches from the standpoint of hormonal (aldosterone and FGF23) and mineral/electrolyte factors (phosphate) as well as iron status appear to be a promising strategy and could constitute a mainstay in the treatment of cardiovascular disorders in CKD.

Abbreviations

ACE2: Angiotensin converting enzyme 2; ACTH: Adrenocortical stimulating hormone; CKD: Chronic kidney disease; FGF23: Fibroblast growth factor 23; GFR: Glomerular filtration rate; LV: Left ventricle; NCC: Sodium chloride cotransporter; RAS: Renin-angiotensin system; ROMK: Renal outer medullary potassium channels

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KH and TS designed and wrote the manuscript. YS and SI collected the literature and discussed the contents of the manuscript with TS and KH. All authors read and approved the final version of the manuscript.

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The authors declare that they have no competing interests.

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