Cardiovascular disease (CVD) and the associated rhythm abnormalities manifesting as tachyarrhythmias, such as atrial fibrillation (AF), continue as leading causes of morbidity and mortality in the United States and developed countries. In spite of the exciting momentum of new discoveries that have greatly improved our understanding of several key molecular mechanisms underlying AF, identifying and managing AF during its early onset stage is extremely challenging. Traditionally, direct causes for CVD have been attributed primarily to genes, ischemic heart disease, poor dietary choices, and lack of exercise; studies later revealed that diseases such as high blood pressure, diabetes mellitus, obesity, and chronic kidney disease (CKD) are powerful risk factors that can equally impact the heart and cause pathologic structural remodeling, contractile dysfunction, hypertrophy, and heart failure, which are well-established substrates for AF.

Of these, CKD has emerged as one of the most potent risk factors for developing CVD and particularly AF. In fact, the high rates of mortality reported in patients with CKD are mainly attributed to cardiovascular complications, including uremic cardiomyopathy or vascular calcifications leading to cardiac complications. Although the reciprocal cross-talk between dysfunctions of kidney and heart is well known, very few common mechanisms have been conclusively identified that could be targeted to impact both CKD and CVD. In this context, fibroblast growth factor 23 (FGF23), a recently described phosphate-regulating hormone secreted by osteocytes and osteoblasts, draws attention. FGF23 works via fibroblast growth factor receptors or specialized Klotho receptors to reduce gastrointestinal phosphate absorption and stimulate renal phosphate elimination. Its expression is positively linked to CKD, wherein FGF23 levels increase during the early stages of CKD and are believed to play a role in increasing urinary phosphate excretion. Elevated FGF23 levels are also associated with the progression of kidney disease and end-stage renal failure, as well as vascular calcifications and increased ventricular mass. Thus, FGF23 has emerged in recent years as a dependable serum biomarker of early alterations in phosphate and bone metabolism, indicating decreasing or worsening kidney function in patients with CKD.

The current dilemma is to determine whether the increased FGF23 expression by itself can cause any of the associated off-target dysfunctions, mainly CVD. Although several clinical studies have reported positive, dose-dependent correlations between FGF23 expression and CVD, other than ventricular hypertrophy, a direct mechanistic effect of FGF23 on other aspects of cardiac dysfunction, specifically AF, is yet to be identified. Seiler et al have shown that FGF23 levels are associated with left ventricular function and AF, even in the absence of renal function impairment, implicating a broader role for FGF23 in CVD and AF. However, it is unclear whether FGF23 acts directly on the myocardium to cause AF. At this juncture, in this issue of Circulation, Mathew et al have presented data from 2 large community-based cohorts, the Multi-Ethnic Study of Atherosclerosis and the Cardiovascular Health Study, to implicate FGF23 in incident AF. This report presents a direct correlation between increased FGF23 levels and the incidence of AF, thereby implicating altered mineral imbalance and kidney dysfunction in creating a susceptibility to AF. A major strength of this study is that the associations were detected in patients with no previous CVD, which indicates that FGF23 levels could be a novel marker for abnormal mineral metabolism (a risk factor for CVD), even in the absence of other known CKD markers, such as epidermal growth factor receptor and urine albumin:creatinine ratio, as well as heart failure symptoms. Moreover, they also show that new-onset AF is correlated with increasing FGF23 levels in populations without previous CVD, implicating a temporal relationship between AF and higher FGF23 expression. This finding could have significant diagnostic value for early prediction of AF risk. As in most cases of AF, arrhythmogenic substrates remain undetected because of the limitations of currently available diagnostic testing options. Based on the data presented by Mathew et al, increasing FGF23 levels could potentially indicate a critical window within the temporal course of incident AF that could be clinically valuable to begin early treatment options to specifically prevent the development of AF substrate.

These findings also present novel directions to better understand FGF23 biology and its role in AF. Although several causal mechanisms have been shown to underlie AF pathology, including autonomic imbalance, cardiac ion channels, upregulation or downregulation of gap junctions and autonomic receptor proteins, and intracellular calcium cycling, pathologic fibrotic remodeling of the atrial myocardium and associated conduction abnormalities are the leading causes.
of a worsening prognosis for patients with AF.\textsuperscript{2,9} The study by Mathew et al\textsuperscript{8} also shows a strong association between higher FGF23 and N-terminal pro-brain natriuretic peptide, a sensitive marker for myocardial wall tension and hemodynamic stress, which are in turn associated with incident AF. Although the authors could not directly show evidence for arrhythmogenic atrial myocardial fibrosis, such pathologic remodeling of the atria can develop in parallel to the observed increase in ventricular mass. In light of all of the available data that implicate FGF23 in AF etiology, it would be important to determine whether FGF23 affects the structure or function of the atrium either directly or secondary to ventricular remodeling to conclusively establish this intriguing bone hormone in arrhythmogenesis.

The most convincing data linking FGF23 with ventricular hypertrophy come from mouse models of CKD, which have shown a direct role for FGF23 in causing cardiac hypertrophy.\textsuperscript{16} Although several mechanisms can be assigned to induce cardiac hypertrophy, altered calcium cycling within the cardiomyocyte has been well documented to play a causal role in triggered arrhythmias (especially AF), as well as cardiac hypertrophy and heart failure.\textsuperscript{11} Interestingly, a recent study indicates that FGF23 can also contribute to altered intracellular calcium dynamics, which affect contractility and induce cardiac hypertrophy,\textsuperscript{12} thereby presenting a novel mechanism by which FGF23 can be arrhythmogenic either by directly modifying calcium cycling or by creating substrates via structural remodeling that can facilitate AF. These are very attractive hypotheses that can potentially identify new mechanisms to explain the connection between FGF23 and rhythm abnormalities associated with CVD. However, they need to be further tested, particularly in the known animal models of altered FGF23 signaling, to target specific molecular mechanisms involved in FGF23-associated AF and to corroborate them with findings from large, community-wide clinical studies.

More importantly, the role of FGF23 in developing a structural and functional AF substrate has to be established specifically in the human atrial myocardium to substantiate future studies, as well as to design treatment options via its signaling pathway; one option is to use explanted human atrial tissue, both with and without structural heart disease, first to determine the presence of specific receptors to FGF23 and whether activation of the cardiac-specific FGF23 signaling in the heart has a direct role in the development of AF. These studies can specifically identify the causal role of FGF23 in facilitating AF via structural substrates or cellular mechanisms of AF. Moreover, other vascular impairments, including calcifications subsequent to the abnormal mineral metabolism associated with FGF23, cannot be discounted to play additive roles in promoting AF, secondary to direct effects on the heart.

One of the fascinating aspects of FGF23 function is its role in the complex mineral-bone disorder characteristic of chronic CKD, wherein FGF23 levels fluctuate positively with the parathyroid hormone, as well as with phosphate levels, but tend to be negatively correlated with 1,25-dihydroxyvitamin D (the active vitamin D hormone), estimated glomerular filtration rate and tubular phosphate reabsorption.\textsuperscript{13,14} Of these, vitamin D via its receptor has been shown to reduce blood pressure and adverse cardiac remodeling including myocardial fibrosis and left ventricular diastolic dysfunction in an experimental animal model of pressure overload.\textsuperscript{15} In light of these findings, increased FGF23 could hypothetically influence cardiac remodeling and increase blood pressure by decreasing vitamin D levels, which could in turn form vulnerable substrates for AF development. The data also implicate the vitamin D pathway as a potential mechanism for AF progression secondary to FGF23 elevation, which definitely warrants further investigation, potentially in existing mouse models of an altered vitamin D pathway. These studies may determine whether restoring vitamin D levels in patients with elevated FGF23 levels can circumvent the deleterious effects of high FGF23\textsuperscript{14} and decrease the incidence of AF.

The current study by Mathew et al\textsuperscript{8} and previously available data, both from basic and clinical studies, conclusively show that FGF23 plays a role in both CKD and CVD via a renal-mineral metabolism axis that could play an important part in either causing or worsening AF. However, the details of this complicated interplay within and between multiorgans spanning the bone-mineral-kidney-heart axis are far from clear; the source and direction of dysfunction in a complicated disease setting such as mineral imbalance and its broad range effects are especially challenging to decipher. Despite all of the existing data, the fundamental question as to whether FGF23 directly causes any of the implicated disorders, including kidney malfunction, bone-mineral imbalances, CVD and AF, or is a beneficial compensatory response that is secondarily recruited to play catalytic roles in other pathways (eg, vitamin D metabolism) known to directly affect cardiac structure and function is yet to be determined. Mathew et al\textsuperscript{8} have quite clearly delineated a strong association between rising FGF23 levels and incident AF, thereby emphasizing its importance as a potential pathway that could be used as a novel risk factor for AF. Future investigations should focus on understanding the fundamental role that it plays in the heart to identify its true contribution to AF development.

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None.

References


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