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Mini Review

Can Fibroblast Growth Factor-23 Improve Prognostication in Heart Failure Patients?

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Abstract

Fibroblast growth factor-23 (FGF-23) is a phosphate regulatory 251-amino-acid hormone secreted by osteocytes and acts as regulator phosphorus re-absorption in the proximal tubule of nephron and 1,25-dihydroxyvitamin D synthesis. Recent clinical studies have shown that higher serum FGF-23 levels are associated with subclinical cardiovascular (CV) disease, with new Heart Failure (HF) and chronic kidney disease. Moreover, FGF-23 is independent and specific predictor of all-cause mortality and CV mortality in general population, subjects with known CV disease and CKD independently traditional CV risk factors. The mini review summarizes knowledge about the predictive role of FGF-23 in HF patient population. In has been suggested that elevated serum FGF-23 may predict CV mortality in HF subjects with reduced left ventricular ejection fraction treated with ACE inhibitors. Moreover, FGF-23 demonstrated an increased discriminatory power for mortality in addition to N-terminal pro B-type natriuretic peptide in HF individuals. Nevertheless, the future studies might explain the predictive value of serial measurements of serum FGF-23 levels and predictive superiority of elevated FGF-23 before other recommended biomarkers, e.g. galectin-3, ST2, and natriuretic peptides. The role of FGF-23 in biomarker-guided care of HF is not still clear and requires more investigations.

Keywords: Fibroblast Growth Factor-23; Heart failure; Cardiovascular disease; Clinical outcomes; Prediction

Introduction

Heart Failure (HF) remains a major cause of cardiovascular (CV) mortality and morbidity worldwide [1]. Despite there are significant recent advances in the medical care of HF, the ability to characterize of the stage, to monitor a patient's response to HF therapy, and to predict clinical outcomes is poor and requires improvement [2]. Over the two last decades, biomarkers of HF have been extensively investigated, particularly for diagnosis and risk stratification [3-5]. Although natriuretic peptides are endorsed by current guidelines and are the gold standard HF biomarker with diagnostic and predictive values [6,7], they are plagued by their non-specific nature [8]. Indeed, the moderate interaction of natriuretic peptides with age, sex, hypervolemic state, and several co-morbidities including myocardial infarction, atrial fibrillation, diabetes, obesity, cardiac hypertrophy, renal failure, has found in recent investigations and today it is well known. In this context, an assessment of HF prognosis beyond the established clinical features / comorbidities and natriuretic peptides seems to be attractive [9]. An assay of additional biomarkers has emerged, however, reflecting different pathophysiological processes and stages in the development of HF, i.e. myocardial injury, inflammation response, reparation and cardiovascular remodeling [10,11], but there is no single biomarker showing high sensitivity and specificity for diagnosing and assessing the severity of HF. Multiple marker strategy is considered an alternate model of routine natriuretic peptide use in this settings, however the optimal number and names of biomarkers are not still defined.

Multiple candidate biological markers indicative of other physiologic aspects of HF development have been identified and scrutinized, including high-sensitivity specific cardiac troponins, soluble ST2, galectin-3, neprilysin, Growth Differentiation Factor-15, and Fibroblast Growth Factor-23 (FGF-23) [12-14]. These biomarkers have been shown arising capacity in determining prognosis beyond the established natriuretic peptides, but their role in the clinical care of the patient is still partially defined and more studies are needed [15,16]. The aim of the mini review is summary of knowledge around ability of FGF-23 to improve predictive value of contemporary model based on use natriuretic peptides in HF individuals.

Biology and Function of Fibroblast Growth Factor-23

FGF-23 is phosphate-regulating 251-amino-acid protein secreted by osteocytes and regulates mineral metabolism and inflammatory response [17]. FGF-23 circulates in both active (intact, iFGF23) and inactive (C-terminal, cFGF23) forms.

FGF-23 increases urinary phosphorus excretion by decreasing phosphorus re-absorption in the proximal tubule of nephron and inhibits 1.25-dihydroxyvitamin D synthesis, resulting in decreased dietary phosphorus absorption from the gastrointestinal tract. Therefore, biological role of FGF-23 affects a secretion of parathyroid hormone [18,19].

Serum FGF-23 concentrations are substantially elevated in rare phosphate wasting disorders, such as hypophosphatemic rickets and tumor induced osteomalacia, as well as in chronic kidney disease [20]. Indeed, elevated iFGF23 levels are observed in a number of

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hypophosphatemic disorders, such as X-linked, autosomal recessive and autosomal dominant hypophosphatemic rickets, whereas low iFGF23 levels are found in the hyperphosphatemic disorder familial tumoral calcinosis/hyperphosphatemic hyperostosis syndrome. All these findings explain the pivotal role of FGF-23 in regulation of phosphate and vitamin D homeostasis.

Recent findings show that iron deficiency and inflammation regulate FGF-23 release and/or biodegradation. It has been found that reduced serum phosphate was accompanied by increased urinary fractional excretion of phosphate, decreased calcitriol levels, and increased parathyroid hormone levels. These findings suggest that iron deficiency increases FGF-23 levels, and that certain iron preparations temporarily increase intact FGF-23 levels [21]. Therefore, serum ionized calcium, insulin growth-like factor 1, and insulin were found as modulators of greater FGF23 concentrations beyond phosphate excretion [18]. Bożentowicz-Wikarek et al., [22] reported that low iron levels are associated with increased levels of both c-terminal FGF-23 and intact FGF-23, independent of low grade inflammation. Thus, iron deficiency stimulates FGF-23 transcription but does not result in hypophosphatemia because FGF-23 is cleaved within osteocytes by an unknown catabolic system. At the same time, phosphate metabolism, intestinal phosphate absorption, iron deficiency, and low-grade inflammation are not the only factors that could be responsible for driving increases in circulating FGF-23 in subjects with chronic kidney disease and normal renal function. For example, serum FGF-23 concentrations are elevated in patients with advanced-stage epithelial ovarian cancer without reductions in serum phosphate concentrations [23].

The exactly mechanisms leading to increased FGF-23 are not fully investigated. There are evidences that hypoxia and ischemia through unknown mechanisms may induce FGF-23 over production in critical ill patients and in those who are underwent cardiopulmonary bypass [24]. Therefore, circulating level of FGF-23 might be elevated due to worsening of kidney clearance especially in acute kidney injury [24,25], while FGF-23 was not determined an early marker of chronic kidney disease [26].

It is suggested that FGF-23 may effect on target cells directly and through FGF-23-related effects. Indeed, in animal models FGF-23 directly stimulated left ventricular hypertrophy by activating hypertrophic gene programs, promoting cardiomyocyte growth, and stimulating the release of natriuretic peptides [27,28]. FGF-23 also inhibits 1.25-dihydroxyvitamin D via effects on CYP27B1 and CYP24A1 enzymes, stimulates the renin-angiotensin system via binding with Klotho, which is a key cofactor for FGF-23 [17]. In animal models Klotho is linked with an advanced aging phenotype [29]. Recent findings have shown that iron deficiency and serum phosphate level were potential mediators of FGF-23 expression [30]. Moreover, human vascular tissue expresses FGF-23 receptors and Klotho [28] and some Klotho gene polymorphisms are associated with CV diseases in humans [31].

Fibroblast Growth Factor-23 and Cardiovascular Risk

Animal and clinical studies have demonstrated direct and indirect effects of FGF-23 of target organs that may promote CV including ischemic heart disease, stroke, HF, and atrial fibrillation and kidney diseases. In fact, higher FGF-23 levels are associated with an increased risk of mortality in CV and kidney diseases and HF development [28,32,33] relating mineral metabolism, cardiovascular remodeling and inflammation [28]. There is a large of body of controversial data that FGF-23 plays a pivotal role in the development of endothelial dysfunction, left ventricular hypertrophy, atherosclerosis, carotid artery intima-media thicknesses, myocardial infarction, and stroke [33-37]. Kestenbaum et al [38] reported that higher serum FGF-23 concentrations were associated with subclinical cardiac disease and with new HF and coronary disease events, but not with carotid intima-media thickness or stroke in the general population. Ix et al [39] presented data clarified that FGF-23 might predict death and CV events in community-living individuals. There are data that in the community older subjects elevated level of FGF-23 associates with atherosclerosis and coronary artery disease mortality [40,41]. A study of 795 general older Swedish adults reported associations of higher serum FGF-23 concentrations with a greater prevalence of cardiac hypertrophy, assessed by echocardiography [42]. Interestingly that FGF-23 was closely related with risks of CV mortality, amputation, or stroke in patients with end-stage chronic kidney disease (CKD) [43,44], although the role of parathyroid hormone and phosphorus in risk modulation of coronary heart disease among this patient population cannot be ignored. In fact, in contrary, a case-control study of male participants in the Health Professionals Follow-up Study found no association of serum FGF-23 level with a composite clinical outcome of non-fatal myocardial infarction and fatal coronary artery disease [45]. Moreover, FGF-23 was not associated with stroke in a sub-analysis of individual events with CKD [46], while relation of elevated level of FGF-23 with sudden cardiac death and atrial fibrillation was found [47,48].

Thus, FGF-23 strongly and independently predicts all-cause mortality, CV events, and end-stage of CKD (ESRD) in general population and in subjects with known ischemic artery disease and CKD (including populations with pre-dialysis CKD, ESRD on hemodialysis, and kidney transplant recipients).

Predictive Value of Preoperative Fibroblast Growth Factor-23 in Acute Kidney Injury Beyond Chronic Kidney Disease

Because performing cardiac surgery with cardiopulmonary bypass is associated with a significant incidence of acute kidney injury (AKI) that is carries a large burden of morbidity and in-hospital mortality, early diagnosis of AKI may lead to better strategies of clinical care [49]. It is well known that circulating FGF-23 levels rise rapidly during AKI in humans independent of parathyroid hormone, vitamin D signaling pathways, and dietary phosphate [50,51]. The potential mechanisms include: increased production of FGF-23 in the bone by yet-to-be-identified factors; ectopic production of FGF-23 by injured renal tubules; and decreased renal clearance of circulating FGF-23 [51]. In this context, FGF-23 may serve as a pre-operative prognostic indicator of the development of AKI following cardiopulmonary bypass surgery [52,53]. Interestingly, that identifying patients more likely to have AKI following surgery provides a means of achieving closer clinical management of AKI and fluid balance. More clinical and experimental studies are required to

validate the use of circulating FGF-23 as a biomarker for the early identification of AKI and prediction of short- and long-term adverse outcomes post-AKI.

Predictive Value of Fibroblast Growth Factor-23 in Heart Failure

Recent clinical studies have shown that elevated FGF-23 was associated more strongly with HF than with atherosclerotic events, and uniformly was associated with greater risk of HF events across subgroups stratified by CKD, eGFR, proteinuria, prior heart disease, diabetes, BP control, anemia, sodium intake, income, fat-free mass, left ventricular mass index, and ejection fraction [54,55]. Wohlfahrt et al., [56] reported that elevated FGF-23 was an independent predictor of adverse events (e.g., death, urgent heart transplantation, ventricular assist device implantation), particularly in HF patients with preserved renal function. Authors suggested that an association of FGF-23 with clinical outcomes probably reflects early alterations of renal hemodynamics and renin-angiotensin system activation, and that elevated FGF-23 level might identify a subset of HF patients benefiting from ACE inhibitor therapy. A study of 980 HF patients enrolled in the Ludwigshafen Risk and Cardiovascular Health study (including 511 patients with reduced ejection fraction HF [HFrEF] and 469 patients with preserved ejection fraction HF [HFpEF] and a median follow-up time of 8.6 years) reported that FGF-23 demonstrated an increased discriminatory power for mortality in addition to N-terminal pro B-type natriuretic peptide in HF individuals with HFrEF, but not in HFpEF [57]. Investigators suggested FGF-23 testing might be relevant in HF patients for risk stratification. However, the perspectives regarding personalized selection of HF treatment based on measurement of serum FGF-23 level are not clear.

Recent clinical studies have shown that increased serum FGF-23 was closely associated with LV hypertrophy, LV diastolic dysfunction, a rise in LV filling pressures, and atrial fibrillation [58-60]. Moreover, data from the Multi-Ethnic Study of Atherosclerosis (MESA) and Cardiovascular Health Study (CHS) showed an association between circulating FGF-23 concentration and incident AF [58]. It has been suggested that higher circulating FGF-23 concentration is associated with incident atrial fibrillation and may partially explain the link between HF and atrial fibrillation [61]. In EPIC-Germany case-cohort study the risk of manifestation of HF, myocardial infarction, but not ischemic stroke in subjects with higher level of circulation FGF-23 was defined [62]. Probably, FGF-23 could help to stratify the HF patients without classical CV risk factors and individualize the medical care. Further studies are required to confirm these results and to identify underlying mechanisms between FGF-23 and HF development and progression.

Conclusion

Higher FGF23 is sufficiently associated with the subsequent development of CV disease, and perhaps most notably HF. However, FGF-23 is independent and specific predictor of all-cause mortality and CV mortality in general population, subjects with known CV disease and CKD and in patients with HFrEF independently traditional CV risk factors and beyond CKD. It seems to be the future studies might explain the predictive value of serial measurements of serum FGF-23 levels and predictive superiority of elevated FGF-23 before other routine used biomarkers, e.g. galectin-3, ST2, and natriuretic peptides. The role of FGF-23 in biomarker-guided care of HF is not still clear and requires more investigations.

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