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REVIEW

Is Fibroblast growth factor 23 the leading cause of increased mortality among chronic kidney disease patients? A narrative review

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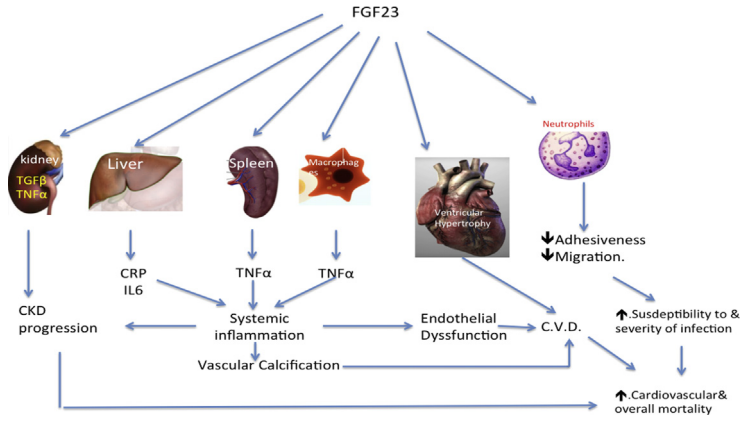
GRAPHICAL ABSTRACT



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ABSTRACT

The death rate among chronic kidney disease patients is the highest compared to other chronic diseases. 60% of these fatalities are cardiovascular. Cardiovascular calcifications and chronic inflammation affect almost all chronic kidney disease patients and are associated with cardio-

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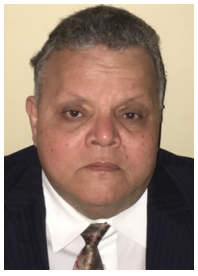
vascular mortality. Fibroblast growth factor 23 is associated with vascular calcification. Systemic inflammation in chronic kidney disease patients is multifactorial. The role of systemic inflammation in the pathogenesis of vascular calcification was recently reappraised. Fibroblast growth factor 23 was accused as a direct stimulus of left ventricular hypertrophy, uremic inflammation, and impaired neutrophil function. This review will discuss the underlying mechanisms that underlie the link between Fibroblast growth factor 23 and increased mortality encountered among chronic kidney disease patients.



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Introduction

Fibroblast growth factor 23 (FGF23) is a member of a large family of structurally related polypeptide growth factors found in different species including humans [1]. Its main function is to regulate serum phosphate level [2]. The serum level of FGF23 starts to rise in early chronic kidney disease (CKD) [3]. By the time of starting dialysis, this level reaches hundred to thousand folds the normal level [4]. According to its role in phosphate metabolism, it was initially thought that the rise of FGF23 in serum carries a favorable effect on bone metabolism and cardiovascular welfare. However, subsequent research disclosed a significant association between FGF23 and vascular calcification (VC) [5,6], left ventricular hypertrophy (LVH) [7], and mortality [8,9] among CKD patients. To further complicate this puzzle, neutralization of FGF23 in CKD rats using monoclonal antibodies accelerated VC and increased mortality [10]. This raised the question whether FGF23 is a friend or a foe? [11,12].

The story of FGF23

FGF23 was identified 16 years ago as a member of FGF family [13]. FGFs are a group of polypeptide growth factors that are involved in metabolic, developmental, neoplastic, and neurologic disorders [14]. The human FGF gene has 22 members, namely FGF1 to FGF14 and FGF16 to FGF23. Humans lack FGF15 [15]. FGF23 exerts its hypophosphatemic effect through inhibition of the luminal sodium-phosphate co-transporters in the proximal tubular epithelial cells [2]. The affinity of FGF23 for its ubiquitous FGF receptors (FGFR) is enhanced by α klotho [16]. FGF23 inhibits 1-α-hydroxylase activity and thus decreases 1,25$(OH)_2$ vitamin D level and increases serum parathormone (PTH) level [2,17].

Vascular calcification in CKD patients

In a prospective observational 3 years follow-up study, the prevalence of VC among predialysis CKD stage G3-5 patients was 79% [18]. It approaches 100% in prevalent dialysis patients [5]. VC affects almost all arteries whether large, medium or small-sized, including the coronary arteries [5,19]. *In vivo* molecular imaging techniques has disclosed that VC is preceded by inflammation within arterial wall [20,21]. A similar finding was confirmed by a longitudinal study using PET/CT scan [22]. VC is one of the predictors of increased cardiovascular mortality among CKD patients [23].

Inflammation in CKD patients

Systemic inflammation is one of the hallmarks of CKD. The exact pathogenesis of inflammation in CKD was not fully understood. Multiple comorbid conditions (like infections and autoimmune systemic diseases) can underlie inflammation in some CKD cases [24]. Blood translocation of bacteria and uremic toxins was recently suggested as an alternative mechanism of uremic chronic inflammation [25]. Lastly, Singh et al., demonstrated that FGF23 stimulates hepatocytes to increase secretion of the inflammatory markers IL6 and C-reactive protein (CRP) [26]. Many of the inflammatory markers and mediators can promote VC in CKD patients. These factors include interleukin 1 (IL-1), IL-6, CRP and tumor necrosis