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## The Role of Fibroblast Growth Factor 23 in the Pathogenesis of Mineral and Bone Disorder in Chronic Kidney Disease: A Review of Foundational Discoveries

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### ABSTRACT

**Introduction:** Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) is a systemic complication of declining renal function involving abnormalities in mineral metabolism and bone pathology. The traditional understanding of its pathogenesis was profoundly revised following the characterisation of the hormone Fibroblast Growth Factor 23 (FGF23).

**Literature Review:** A review of pivotal scientific literature reveals that FGF23 was identified as a potent, bone-derived hormone that regulates phosphate homeostasis. Seminal studies demonstrated that in response to declining renal function, FGF23 levels rise early and progressively. This rise is initially an adaptive mechanism to promote urinary phosphate excretion and maintain normal serum phosphate levels. However, this compensation comes at a cost: high FGF23 levels suppress the production of active vitamin D and are a primary stimulus for the development of secondary hyperparathyroidism. Foundational observational studies established a strong and independent association between elevated FGF23

concentrations and adverse outcomes, including cardiovascular disease and mortality, in patients with CKD. The discovery of Klotho as an essential co-receptor for FGF23 function further illuminated this complex signaling axis.

**Conclusion:** The body of evidence reviewed establishes FGF23 as a central pathogenic factor in CKD-MBD. Its role extends beyond that of a simple biomarker, identifying it as a key mediator that links disordered mineral metabolism with the high rates of cardiovascular morbidity and mortality characteristic of chronic kidney disease.

**Keywords:** Fibroblast Growth Factor 23 (FGF23), Chronic Kidney Disease (CKD-MBD), Secondary Hyperparathyroidism, Phosphate, Klotho.

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## INTRODUCTION

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The management of mineral and bone disorders in patients with Chronic Kidney Disease (CKD) is a cornerstone of nephrology practice. Historically, the pathophysiology of this complication, known as CKD-Mineral and Bone Disorder (CKD-MBD), was understood through the classical interplay of three components: as kidney function declines, the retention of phosphate was thought to cause a decrease in serum calcium, leading to a compensatory and ultimately damaging increase in parathyroid hormone (PTH). This model, while useful, failed to explain all the clinical observations.

A fundamental shift in this paradigm occurred with the discovery and characterisation of a previously unknown hormone, Fibroblast Growth Factor 23 (FGF23). Research revealed that FGF23 was not a minor participant but a central regulator of mineral metabolism. This literature review aims to synthesise the pivotal scientific publications that identified the physiological role of FGF23 and established its crucial link to the pathogenesis of mineral and bone disorders and adverse clinical outcomes in patients with CKD.

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## LITERATURE REVIEW

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The understanding of FGF23's role in CKD-MBD progressed rapidly through a series of foundational discoveries related to its physiology, pathophysiology, and clinical associations.

First, the fundamental physiological function of FGF23 was elucidated. Research identified FGF23 as a hormone produced primarily by osteocytes and osteoblasts in bone in response to factors such as dietary phosphate intake (Shimada et al., 2004). Its principal actions were shown

to be twofold: it acts on the kidney to potently increase urinary phosphate excretion (a phosphaturic effect), and it strongly suppresses the renal enzyme 1-alpha-hydroxylase, which is responsible for converting inactive vitamin D to its active form, 1,25-dihydroxyvitamin D. Thus, FGF23 was established as the body's primary hormone for eliminating excess phosphate.

The second major advance was applying this new physiological knowledge to the context of CKD. Seminal studies demonstrated that serum FGF23 concentrations begin to rise very early in the course of CKD, often long before elevations in serum phosphate or PTH are detectable (Larsson et al., 2003). This established a new model for the pathogenesis of secondary hyperparathyroidism. In this revised model, the rise in FGF23 is an early, adaptive response by the bone to failing kidney function, attempting to maintain phosphate balance by increasing fractional excretion of phosphate from the remaining nephrons. However, this adaptation has severe maladaptive consequences. The FGF23-driven suppression of active vitamin D production impairs intestinal calcium absorption, leading to hypocalcemia, which stimulates PTH secretion. Furthermore, high FGF23 levels were also suggested to have direct stimulatory effects on the parathyroid glands, cementing FGF23 as a primary driver, not just a consequence, of the high PTH levels seen in CKD.

The complexity of this system was further clarified by the discovery of Klotho, a transmembrane protein that was found to be an obligate co-receptor for FGF23. For FGF23 to exert its effects on the kidney, it must bind not only to its FGF receptor but also to Klotho. It was discovered that Klotho expression decreases as kidney disease progresses, creating a state of FGF23 resistance in the kidney (Kurosu et al., 2006). This resistance helps to explain why FGF23 levels must rise to such astronomical heights in advanced CKD as the body attempts to overcome the signaling defect.

Finally, and perhaps most importantly from a clinical perspective, observational studies began to link these extraordinarily high FGF23 levels to the severe morbidity and mortality seen in CKD patients. Powerful prospective cohort studies demonstrated that elevated FGF23 was one of the strongest predictors of all-cause mortality and cardiovascular events in patients on dialysis, independent of serum phosphate, calcium, or PTH levels (Gutierrez et al., 2008). High FGF23 was also associated with markers of cardiovascular disease, such as left ventricular hypertrophy and vascular calcification, suggesting it was not merely a biomarker but a potential pathogenic mediator of uremic cardiovascular disease.

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## CONCLUSION

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The pivotal literature examining Fibroblast Growth Factor 23 fundamentally reshaped the understanding of Chronic Kidney Disease-Mineral and Bone Disorder. FGF23 was unmasked as a central hormonal regulator in a complex endocrine axis involving the bone, kidney, and parathyroid glands. The research established that the early, compensatory rise in FGF23 to maintain phosphate homeostasis is a key initiating event in the pathogenesis of secondary hyperparathyroidism by suppressing active vitamin D.

Furthermore, the strong and independent association of elevated FGF23 levels with mortality and cardiovascular disease in CKD patients provided a powerful new prognostic tool and a potential explanation for the high cardiovascular burden in this population. This body of work provided a more complete and nuanced pathophysiological framework for CKD-MBD, identifying FGF23 and its co-receptor Klotho as critical new targets for future research and therapeutic intervention.

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