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Meta-organismal tryptophan metabolism: an appealing therapeutic target in CKD-MBD

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Abstract

Despite important advances over the past few decades, chronic kidney disease-mineral and bone disorder remains a major clinical therapeutic challenge. Traditional interventions targeting hyperphosphatemia, impaired vitamin D metabolism, and secondary hyperparathyroidism overall failed to meet expectations. This calls for a paradigm shift. The 2023 Madrid Chronic Kidney Disease-Mineral and Bone Disorder Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference advocated a holistic approach to replace the current parathyroid hormone-calcium phosphate-centric approach. In this context, the fibroblast growth factor 23-α-Klotho axis has emerged as a key regulator of mineral metabolism and a potential novel therapeutic target. In parallel, meta-organismal tryptophan dysmetabolism recently gained interest as a novel pathogenic driver of both chronic kidney disease-associated osteoporosis and cardiovascular disease. Chronic kidney disease not only profoundly disturbs microbial and endogenous tryptophan metabolism, but also causes accumulation of tryptophan metabolites, some of which are increasingly recognized as uremic toxins, including indoxyl sulfate, kynurenine, and kynurenic acid. They may confer cardiovascular and skeletal toxicity either by inducing direct cellular toxicity or by activating the aryl hydrocarbon receptor. While adding another level of complexity to the pathogenesis of chronic kidney disease-mineral and bone disorder, these insights also create novel therapeutic opportunities.

Keywords: CKD-MBD; cardiovascular disease; chronic kidney disease; osteoporosis; tryptophan metabolism; uremic toxins.

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