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Review

Effect of uremic toxin-indoxyl sulfate on the skeletal system

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ABSTRACT

Chronic kidney disease-mineral bone disorders (CKD-MBD) exhibit abnormalities in the circulating mineral levels, vitamin D metabolism, and parathyroid function that contribute to the formation of a bone lesion. The uremic toxin, indoxyl sulfate (IS), accumulates in the blood in cases of renal failure and leads to bone loss. The bone and renal responses to the action of the parathyroid hormone (PTH) are progressively decreased in CKD in spite of increasing PTH levels, a condition commonly called PTH resistance. There is a high prevalence of low bone turnover or adynamic bone disease in the early stages of CKD. This could be due to the inhibition of bone turnover, such as in PTH resistance, reduced active vitamin D levels, diabetes, aluminum, and, increased IS. With an increase in IS, there is a decrease in the osteoblast Wnt/b-catenin signaling and increase in the expression of Wnt signaling inhibitors, such as sclerostin and Dickkopf-1 (DKK1). Thus, a majority of early CKD patients exhibit deterioration of bone quality owing to the action of IS, this scenario could be termed uremic osteoporosis. However, this mechanism is complicated and not fully understood. With progressive deterioration in the renal function, IS accumulates along with persistent PTH secretion, potentially leading to high-turnover bone disease because high serum PTH levels have the ability of overriding peripheral PTH resistance and other inhibitory factors of bone formation. Finally, it leads to deterioration in bone quantity with prominent bone resorption in end stage renal disease. Uremic toxins adsorbents may decelerate oxidative stress and improve bone health in CKD patients. This review article focuses on IS and bone loss in CKD patients.

1. Introductions

Chronic kidney disease (CKD) may cause several disorders, including bone and mineral metabolism, previously defined as renal osteodystrophy (ROD). In the recent decade, CKD- mineral bone disorders (MBD), as a broader definition of the abnormalities in systemic bone mineral metabolism and cardiovascular system, comprise three characteristics: laboratory abnormalities, vascular/soft tissue calcification, and bone metabolism deterioration [1]. During CKD progression, uremic toxin retention contributes to several symptoms in the body, termed as uremic syndrome. Among uremic toxins, protein-bound compounds, such as indoxyl sulfate (IS), are difficult to remove via classical dialysis methods because of their strong protein-binding capabilities. In CKD progression, IS can induce the production of TGF-β1, tissue inhibitors of metalloproteinase-1 (TIMP-1), endothelin-1, and osteopontin to promote epithelial-to mesenchymal transition (EMT) [2], ultimately leading to renal tubular and interstitial fibrosis. In the cardiovascular system, IS correlates with pentosidine and high-density lipoprotein cholesterol, risk factors for atherosclerosis in hemodialysis patients [3] (Fig. 1). In addition, IS enters the T cells to deviate the differentiation pathways of T cells to the progress of Th17 direction in adaptive immunity and cause T cells inflammation effects, resulting in immunity disorders.

In the bone, IS can also decrease osteoclast differentiation and

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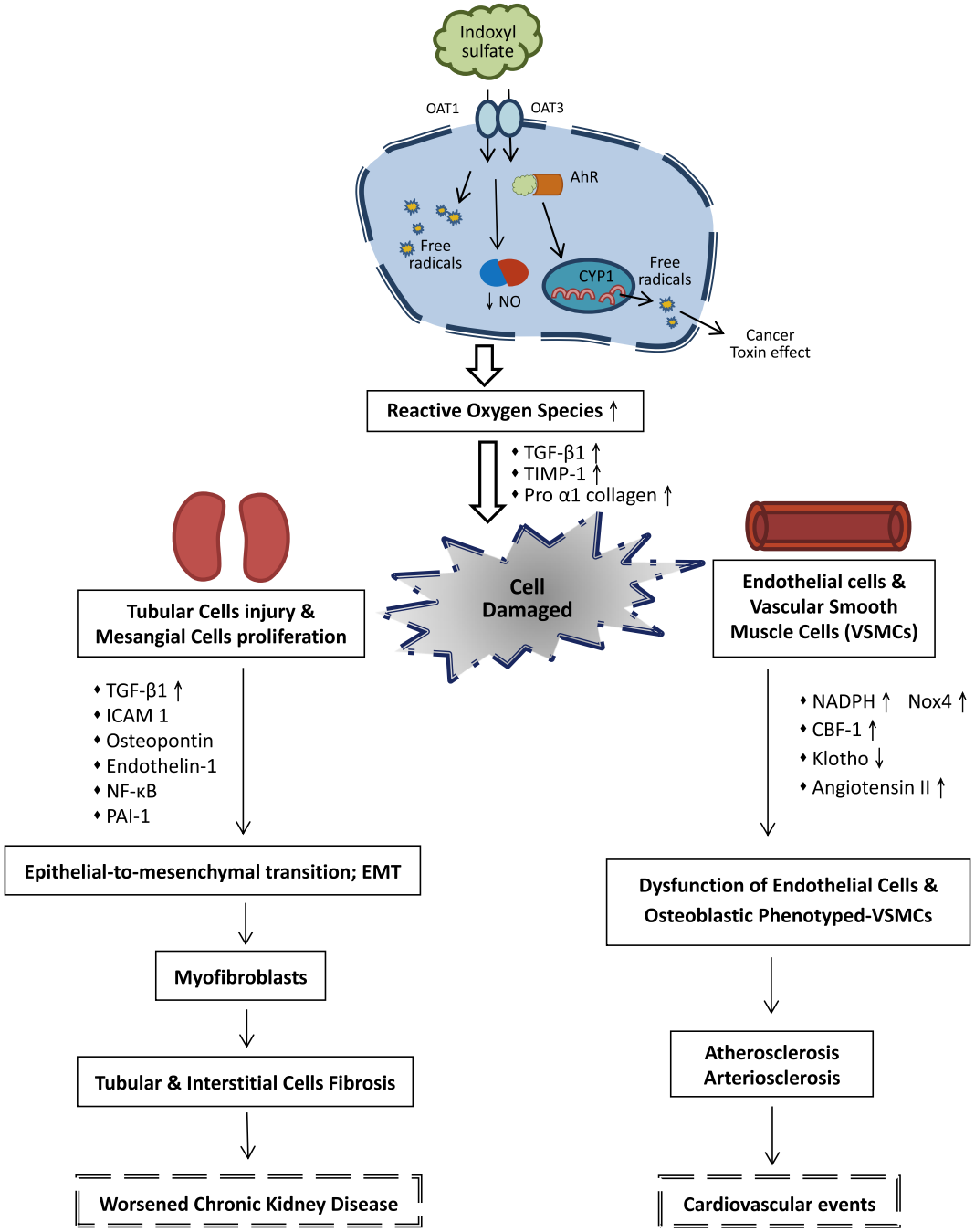

Fig. 1. Nephro-vascular toxicity of indoxyl sulfate. Indoxyl sulfate (IS) enters the renal tubular cells or VSMCs through OAT1 and OAT3. IS induces free radical production, reduces nitric oxide, and activates AHR to produce reactive oxygen species; thereafter, it enhances the secretion of TGF-β1, TIMP-1, and pro α1 collagen to damage the cells. In the kidneys, the injured tubular cells and mesangial cells secrete various cytokines to promote epithelial-to-mesenchymal transition, resulting in tubular and interstitial cells fibrosis. In the cardiovascular system, the damaged endothelial cells and VSMCs increase the secretion of NADPH and Nox4 while decreasing the secretion of klotho to cause dysfunction of the endothelial cells and osteoblastic phenotyped-VSMCs, finally leading to atherosclerosis and arteriosclerosis. NADPH: Nicotinamide adenine dinucleotide phosphate hydrogen; VSMCs: Vascular smooth muscle cells; OAT: Organic anion transporters; AHR: Aryl hydrocarbon receptor; TGF-β1: transforming growth factor-ß1; TIMP-1: tissue inhibitor of metalloproteinase-1; ICAM-1: intercellular adhesion molecule-1; NF-κB: nuclear factor kappa B; PAI-1: plasminogen activator inhibitor-1; CBF-1: core binding factor 1.

promote osteoblast apoptosis. However, it is important to note that bone disorders in CKD patients are not only due to abnormal mineral metabolism that reduces bone quantity, but also due to uremia toxins that have the potential to affect bone quality. Previous studies have shown that majority of early CKD patients present adynamic bone disease or low bone turnover in the beginning of bone deterioration. Furthermore, Fukagawa et al. observed that IS reduces parathyroid hormone (PTH)-stimulated intracellular cyclic adenosine monophosphate (cAMP) production, decreases PTH receptor expression, and induces oxidative stress in the bone cells [4]. They suggest that higher IS levels might be a factor of low bone turnover and adynamic bone disease because it causes skeletal resistance to PTH in CKD patients [4]. Alternatively, the accumulated IS plays another important role in worsening bone mechanical properties by changing the chemical composition of the bone (pentosidine/matrix ratio, mineral/matrix ratio, and carbonate substitution increased) (Fig. 2). This mechanism