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Effect of pharmacologic therapeutics in CKD sarcopenia

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Inflammation, metabolic acidosis, renin-angiotensin system activation, insulin resistance, impaired perfusion to skeletal muscles, etc., are possible causes of uremic sarcopenia. These conditions induce the activation of NF-kB and MAPK pathway, ATP-UPS, and ROS system, resulting in the protein catabolism (decreased protein synthesis and increased protein degradation).

There have been many drugs which were developed to prevent or treat sarcopenia (general). However, only a few of them, i.e., Bimagrumab from Novartis and Sarconeos from Biophytis SAS, reported recent results and showed the effectiveness in terms of adiposity, metabolic disturbances, and walking test in limited criteria of participants in 2021 and 2022.

The main interventions for prevention and treatment of sarcopenia in Chronic kidney disease (CKD) are aerobic and resistance exercises along with nutritional interventions. And optimizing dialysis, vitamin D status, acidosis as well as management of co-morbidities are also mandatory.

CKD impairs the balance between symbionts and pathobionts in a way that favors pathobiont overgrowth. Influx of urea and other retained toxins exerts a change in the gut microbiome in CKD (decreased number of beneficial bacteria producing short-chain fatty acids and increase of bacteria producing uremic toxins such as indoxyl sulfate, p-cresyl sulfate, and trimethylamine-N-oxide). Enhanced permeability of the intestinal barrier allows the passage of endotoxins and other bacterial products to the blood.

Kidney-gut-muscle axis means that dysbiosis and change of gut-derived uremic toxins and short chain fatty acids affect muscle mass, composition, strength, and functional capacity.

Indoxyl sulfate accumulated in muscle cells activates NADPH oxidase and the aryl hydrocarbon receptor pathway to cause increased ROS production. And triggered inflammatory cytokines (TNF-α , IL-6, and TGF-β1) induce myostatin and atrogin-1 expression leading to muscle wasting. Indoxyl sulfate induced mitochondrial network disintegration thorough metabolic alterations, such as upregulation of antioxidative responses and downregulation of energy-generation related pathways in muscle cells, which resulted in reduced ATP production. Indoxyl sulfate associated decreased expression of Klotho in muscles can be a mechanism of muscle mass loss in CKD. Indoxyl sulfate has direct toxic effects on myoblasts by decreasing its viability and increasing cell apoptosis.

Synbiotics changed the microbiota in CKD patients (increase in Bifidobacterium/ Lactobacillus, decrease in Clostridium) and decreased uremic toxins (indoxyl sulfate and p-cresyl sulfate).

AST-120 prevented tissue accumulation of indoxyl sulfate and p-cresyl sulfate. Reduced accumulation of indoxyl sulfate resulted in the amelioration of muscle atrophy. AST-120 improved exercise capacity and mitochondrial biogenesis of skeletal muscle. Reduced exercise capacity, decreased PGC-1α, increased mitochondrial autophagy was restored by AST-120. AST-120 restored the epithelial tight junction proteins and reduced plasma endotoxin and markers of oxidative stress and inflammation. AST-120 administration also changed overall gut microbiota composition in the CKD model.

In a human study, the addition of AST-120 to standard treatment modestly had beneficial effects on

gait speed change and quality of life and showed the potential to improve sarcopenia.

Prospective studies with longer follow-up duration, larger sample size, and interventions of uremic toxin lowering are necessary to elucidate the role of uremic toxin in sarcopenia in CKD patients.