

## Case Reports: Beneficial Roles of Aloe vera Juice-successive Ingestion to Children with Steroid-Sensitive Nephrotic Syndrome

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### ABSTRACT

We present two case reports: beneficial roles of successive ingestion of aloe vera juice for medical treatment of steroid-sensitive nephrotic kidney syndrome in child.

**Key words:** Nephrotic kidney syndrome; Child with steroid-sensitivity; Aloe vera juice-successive ingestion

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### INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of chronic kidney disease (CKD) in children. In most cases, children with idiopathic nephrotic syndrome (INS) are first treated for prednisolone according to international study of kidney disease in children induction protocol. Steroid sensitive nephrotic syndrome (SSNS) is experienced by approximately 90% of all INS patients<sup>[1]</sup>. Oh *et al*<sup>[2]</sup> reviewed steroid-associated side effects in patients with primary proteinuric kidney disease. Bone disorders were infrequently observed in patients with primary proteinuric kidney disease. Steroid-treated patients were 3.6 times as likely to have fractures compared with those not treated with steroids. Large population-based studies have shown higher risks of fractures, especially vertebral fractures, in those exposed to oral corticosteroid therapy even after adjusting for confounding factors such as age, sex coexisting disease, and concomitant medication. Osteoclasts (OCs) are the exclusive bone resorption cell, they derive from monocyte and macrophage precursors, which can circulate within the hematopoietic cell pool or be resident in a number of tissues. The maintenance of an adequate bone mass depends on the controlled and timely removal of old, damaged bone. During the bone resorption process there is an intense cross-talk between immune system cells and OCs. D'Amico and Roato<sup>[3]</sup> review T cells release factors and cytokines, which rule osteoclastogenesis, and OCs produce factors that act on T cells. Sun *et al*<sup>[4]</sup> show gut microbiota-derived short chain fatty acids (SCFAs) promote microbiota antigen-specific Th1 cell IL-10 production, mediated by G-protein coupled receptors 43 (GPR43). The authors provided insight into how microbiota metabolites, SCFAs, regulate Th1 cell functions to maintain intestinal homeostasis. The intestinal microbiota may regulate bone metabolism by reducing levels of pro-inflammatory cytokines, and T cells in bone tissues of estrogen-deficient mice have been reported by Touse *et al*<sup>[5]</sup>. Ovariectomised (OVX) mice fed a 20% acid-hydrolyzed high amylose (AH) corn

starch (HAS)-containing diet accelerated fermentation in the caecum, and increased the abundance of *Bifidobacterium* spp. in feces. The AH-HAS diet tended to upregulate mRNA expression of the anti-inflammatory cytokine IL-10 in the colon, and down regulate expression of the osteoclastogenic cytokine RANKL and IL-7R genes in the bone marrow of OVX mice. AH-HAS treatment attenuated ovariectomy-induced bone loss. The findings suggest that AH-HAS might change the microbiota and immune status of the bone marrow, resulting in attenuated bone resorption in OVX mice.

Since gut microbiota and their metabolites short chain fatty acids (SCFAs) have linked to CKD and hypertension, Hsu *et al*<sup>[1]</sup> examined whether gut microbial composition and SCFAs are correlated with blood pressure (BP) load and renal outcome in CKD children with CAKUT. Reduced plasma level of propionate was found in children with CAKUT, which was related to increased abundance of phylum *Verrucomicrobia*, genus *Akkermanisia*, and species *Bifidobacterium bifidum*. The findings highlight that gut microbiota-derived SCFAs like propionate and butyrate are related to BP abnormality in children with an early stage of CKD. Tsuji *et al*<sup>[6]</sup> exhibited that dysbiosis involving decreased butyric acid-producing gut microbiota leads to defective induction and differentiation of peripherally induced regulatory T cells (T regs), resulting idiopathic nephrotic syndrome (INS) relapse. Pediatric relapsing INS patients show gut microbiota dysbiosis, characterized by a decreased proportion of butyric acid-producing bacteria and lowered fecal butyric acid quantities, concomitant with reduced circulatory T regs. Tyagi *et al*<sup>[7]</sup> show that oral supplementation with the widely used probiotics, *Lactobacillus rhamnosus* (LGG), increases bone mass in mice by increasing the serum levels of the SCFA butyrate. LGG or butyrate increases the frequency of T reg cells in the intestine and in the bone marrow. Interaction of bone marrow CD8<sup>+</sup> T cells with T reg cells resulted in increased secretion of Wnt10b, a bone anabolic Wnt ligand. Thus, butyrate concentrations regulate bone anabolism via T reg cell-mediated regulation of CD8<sup>+</sup> cell Wnt10b production. Wnt10b stimulates bone formation by activating Wnt signaling in osteoblasts. LGG and butyrate may represent new interventions for the prevention and treatment of osteoporosis. Lucas *et al*<sup>[8]</sup> exhibited that therapeutic supplementation of SCFA, propionate and butyrate, or diets increasing the endogenous production of SCFA may provide a powerful instrument to balance osteoclast activity and inhibit bone resorption. Even more importantly in case of inflammatory bone loss the combination of anti-inflammatory immune-regulatory properties of SCFA together with the distinct inhibition of osteoblast activity may be particularly useful. In this connection the benefits of the so-called Mediterranean-type diets, which are rich in fibers causing elevated levels of SCFA in managing human inflammatory arthritis, may be explained. Recently, SCFAs, which are generated by fermentation of complex carbohydrates, have emerged as key regulatory metabolites produced by the gut microbiota<sup>[9]</sup>. Nutritional supplementation with probiotics, such as aloe vera complex carbohydrates, can prevent pathologic bone loss.

## CASE REPORT

### Case report 1: The risk-remission for steroid-induced osteonecrosis of femoral head after nephrotic kidney syndrome in child with successive ingestion of aloe vera juice

A one-year and ten-months boy presented to nephrosis syndrome seven times on June 2007, and was administered cyclosporine (CS) 0.5mg every two times a day and prednisolone (PD) 20 mg every other day. On August 2009, he presented to osteonecrosis of femoral

head, and was inability to walk. Then, he successively ingested aloe vera juice (AVJ) 400 mL per day with administration of CS and PD. On May 2010 the osteonecrosis was slow down, and he was able to walk. On July 2011, the nephrosis relapsed again. He continued to ingest AVJ with CS until January 2013 and achieved a complete remission of nephrosis, showing negative albuminuria. Since then, he is clearly remitted nephrotic kidney syndrome with successive ingestion of AVJ, without any administration of CS and PD.

### Case report 2: The risk-remission for steroid treatment to minimal change nephrotic syndrome

Eight years and 5 months girl presented to minimal change nephrotic syndrome (MCNS) with edema around eyes on August 2011, and was immediately hospitalized. She was administered prednisolone 50mg/day and ingested AVJ 1000 mL per day with supplementation of bee-pollen 17g and propolis 20g every day. After one month hospitalized she was recovered her normal blood standard in albuminuria, cholesterol, and creatinine and remitted MCNS. Since September 2011, she ingested AVJ 1000 mL every day with the supplementation, and had no nephrotic syndrome again. She was completely remitted on November 2019.

## DISCUSSION

SCFA, butyrate, can serves as energetic fuel, modulates gene expression via modification of histone residues, and functions as signaling molecules by binding to receptors and triggering a downstream signaling cascade. The precise therapeutic efficacy is highly dependent on cell type, concentration, tissue context, and receptor expression patterns. Due to butyrate's potential role, it is currently in phase 2 and 3 trials to study its effect on insulin resistance and liver damage in children with obesity (NCT02721953)<sup>[10]</sup>. Minimal change disease (MCD) is one of the more treatable kidney diseases, especially in children. Therapy almost always consists of a course of oral prednisolone, which is generally effective within weeks. Patients with recurrent MCD or MCD that do not completely resolved with prednisolone, may require other forms of therapy. In an earlier paper<sup>[11]</sup> we discussed beneficial roles of aloe fermented butyrate, propionate, and aloin to chronic kidney disease and uremic toxins. As shown in the case report, successive ingestion of aloe vera juice (AVJ) may decrease the risk for the steroid-induced osteonecrosis of femoral head after kidney nephrosis. Aloe vera fermented butyrate may blunt osteoclastogenesis and bone resorption, and stimulate bone formation. Furthermore, AVJ with the supplementation of bee-products may suppress MCNS.

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