



Two-way Regulation of Intestinal Microorganisms on Hyperuricemia and Gout

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Abstract: In recent years, the two-way regulation of intestinal microorganisms in the pathogenesis of hyperuricemia and gout has attracted increasing attention. Studies have shown that specific probiotics can participate in the regulation of uric acid metabolism in many ways, including promoting intestinal uric acid excretion, inhibiting xanthine oxidase activity, enhancing intestinal barrier function and regulating immune inflammatory response, thus effectively reducing blood uric acid level and alleviating the onset of gouty arthritis. On the contrary, colonization or flora imbalance of conditional pathogenic bacteria can induce chronic inflammation, destroy intestinal mucosal barrier, inhibit uric acid excretion, and further aggravate metabolic disorder. Metagenomics further revealed that some intestinal flora can degrade purine metabolites and regulate purine homeostasis. To sum up, intestinal microorganisms affect uric acid homeostasis through metabolism and immunity, forming an interactive network of "flora-metabolism-inflammation". In the future, we should develop individualized intervention strategies based on probiotics, prebiotics and synthetic biology techniques, and provide a new path for the accurate prevention and treatment of hyperuricemia and gout.

Keywords: intestinal microorganisms; hyperuricemia; gout; probiotics

1. Introduction

1.1 Background Introduction

Hyperuricemia (HUA) is a metabolic disease, mainly manifested as purine metabolism disorder and uric acid (UA) excretion disorder [1]. A large-scale baseline data study in Beijing-Tianjin-Hebei region of China in 2022 found that the prevalence of hyperuricemia in men reached 27.72%, that in women was 10.69%, and that in the total population was 19.37%.[2]. Long-term hyperuricemia not only increases the risk of gout, but also significantly increases the risk of kidney damage, cardiovascular disease and other metabolic abnormalities [3], which has become a public health issue that cannot be underestimated.

With the development of multi-omics research, more and more evidences show that [4-6], intestinal microflora plays a vital role in the regulation of uric acid metabolism. The imbalance of intestinal flora is closely related to hyperuricemia. The application of probiotics [7] can regulate the intestinal environment and promote intestinal health, and has the potential to be used as a treatment for related diseases [8].

In recent years, studies have increasingly revealed that intestinal microflora is not only vital to the local health of the intestine, but also closely related to the systemic metabolic function, especially playing an important role in the regulation of uric acid metabolism. Cai et al. found in a cross-sectional study that the risk of hyperuricemia decreased by about 3.2% for every unit increase in the intestinal microbial index related to diet [9]. In addition, supplementing *Lactobacillus paracasei* N1115 to hyperuricemic mice can reduce serum uric acid level by about 29.18%, and its mechanism is related to the increase of intestinal butyrate level and probiotic abundance [10].

When the intestinal microflora is unbalanced, conditional pathogenic bacteria may induce chronic low-grade inflammatory reaction, destroy the integrity of intestinal barrier and disturb immune homeostasis, thus weakening the intestinal excretion ability of uric acid and promoting the accumulation of uric acid in the body. Related studies have pointed out that the imbalance of intestinal microflora may not only weaken the intestinal excretion of uric acid by reducing the production of beneficial SCFA and the expression of intestinal transporters, but also further inhibit the metabolic homeostasis of uric acid by inducing inflammatory reaction [11-12].

To sum up, intestinal microflora has a clear two-way regulation function in uric acid metabolism: on the one hand, probiotics and their products promote intestinal excretion of uric acid and improve metabolic stability; On the other hand, flora imbalance or harmful bacteria proliferation may weaken this mechanism, lead to uric acid accumulation, and then promote hyperuricemia and gout.

1.2 Research purpose

The purpose of this study is to analyze how intestinal microorganisms affect uric acid level by regulating immune response, metabolite production and intestinal barrier function, and further explain the mechanism of intestinal microorganisms on HUA and gout, so as to provide new theoretical basis and intervention strategies for disease prevention and treatment.

2. Two-way regulation of intestinal microorganisms on hyperuricemia and gout

The diversity of intestinal microorganisms is closely related to the health status of the host, and there are two main mechanisms that affect the metabolism of the host: first, SCFAs is produced by probiotics or functional flora, which maintains the intestinal barrier, regulates metabolism and promotes the intestinal excretion of uric acid [13]; Secondly, when the flora is unbalanced, it can damage the intestinal barrier, reduce beneficial metabolites and induce low-grade inflammation, thus inhibiting the normal excretion of uric acid and leading to its accumulation [14]. This logic links "intestinal microflora-short-chain fatty acids-uric acid metabolism" and emphasizes the importance of microbial flora balance in preventing and treating hyperuricemia and its related metabolic abnormalities.

Probiotics have a positive regulatory effect on uric acid metabolism through multiple mechanisms: on the one hand, probiotics can promote the proliferation of beneficial bacteria and inhibit the proliferation of potential pathogenic bacteria, thus improving the integrity of intestinal barrier; On the other hand, its metabolites and related signal pathways can promote the excretion and metabolism of uric acid in intestine and kidney [15], thus helping to reduce the serum uric acid level. For example, *Lactobacillus paracasei* 12 can significantly decrease the serum uric acid level by inhibiting the activity of xanthine oxidase in liver and regulating the expression of uric acid transporter in kidney [16]. In addition, the study also found that *Limosilobacillus reuteri* HCS 02001 can reduce uric acid by regulating mucosal immune system to inhibit metabolic inflammation in hyperuricemic model [17].

Conditional pathogenic bacteria can trigger the activation of host immune system, lead to chronic inflammation, and thus promote the increase of serum uric acid level. Lv et al. pointed out that in hyperuricemia model, the imbalance of intestinal flora is related to the increase of inflammatory factors and uric acid level, and the impairment of intestinal barrier function will also weaken the host's excretion function of uric acid through intestinal and renal pathways by inducing systemic inflammatory reaction [18]. Other studies have also pointed out that when the conditional pathogenic bacteria are over-amplified, it will inhibit the growth of beneficial bacteria, lead to the reduction of short-chain fatty acid production and the imbalance of intestinal microecological products, and then affect the synthesis and excretion path of uric acid [19].

3. The relationship between intestinal microorganisms and uric acid metabolism

Intestinal microflora participates in the regulation of host uric acid metabolism through multiple mechanisms, and its main manifestations can be summarized as the following three aspects:

Affect the synthesis and excretion of uric acid: intestinal microorganisms can indirectly affect the expression and activity of uric acid-producing enzymes in the liver by changing the intestinal environment, thus inhibiting the synthesis of uric acid. In addition, intestinal flora may also regulate the mechanism of uric acid degradation or transport in the intestine, thus affecting uric acid excretion. In patients with hyperuricemia, the imbalance of intestinal flora is related to the abnormal metabolic pathway of uric acid production and degradation [20].

Functional interaction with liver and kidney: Some studies have pointed out that intestinal flora and metabolites affect uric acid metabolism through the axis of intestine, liver and kidney, thus maintaining uric acid homeostasis in vivo [14,21].

Regulating the expression of genes related to uric acid metabolism: Intestinal microorganisms and their metabolites can affect the expression and activity of genes related to uric acid metabolism in liver, kidney or intestine by activating receptors in host cells (such as GPR41/43) or changing signal pathways [14].

Intestinal microflora is not only affected by the uric acid level of the host, but also has a feedback regulation effect on uric acid level. Previous studies have shown that in hyperuricemia model, the diversity of intestinal microflora decreased ($p < 0.01$), and serum uric acid level was positively correlated with intestinal barrier injury index [18]. Miyajima et al.'s research also showed that the α diversity of fecal flora in high uric acid population decreased ($p < 0.001$), suggesting that the change of uric acid level would adversely affect the intestinal flora structure [22].

4. Potential of intestinal microbial intervention in gout management

Probiotics have shown certain efficacy in clinical research by regulating intestinal microecological balance, enhancing immune function and reducing uric acid level [23]. In a randomized controlled RCT, after 6 months of administration of *Lactobacillus salivarius* cect 30632 (9 log cfu/day), the serum uric acid level in the probiotic group decreased significantly

and the number of gout attacks decreased [24].

In addition to probiotic intervention, inhibiting the excessive proliferation of conditional pathogens in intestinal microecology is also an important strategy to regulate the balance of intestinal flora. Studies have shown that it has potential in improving flora structure, reducing endotoxin production, alleviating systemic inflammatory reaction, and then affecting serum uric acid level [25], which can provide an auxiliary path for controlling uric acid level and alleviating hyperuricemia and gout.

5. Conclusion and future prospect

Intestinal microflora not only acts as the "regulator" of uric acid metabolism in the host, but also feeds back the process of uric acid production, excretion and deposition in the host through the changes of its own structure and function. Therefore, regulating intestinal microecology provides a new idea for the prevention and treatment of HUA and gout.

Future research should further explore the combination of precise regulation of intestinal microflora and individualized treatment, focusing on the synergistic effect of intestinal microflora and drug treatment. In addition, the specific target, dosage, duration and safety of antimicrobial agents/prebiotics/dietary intervention should be further clarified, and the different effects of microbial intervention on acute and chronic gout should be discussed and studied.

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