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Advances in the Study of Uric Acid-Related Diseases

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Abstract: *As a key antioxidant in the body, it is strongly tied to the proper metabolism of the human body, and the irregularity of uric acid metabolism can produce a series of pathophysiological changes leading to a range of disorders. In recent years, various investigations have been undertaken regarding uric acid abnormalities. This article mainly elaborates on the study development of uric acid-related disorders from the link between uric acid level and diseases, prognosis, and etiology, with a goal of providing a reference for the management of uric acid.*

Keywords: *uric acid; disease prognosis; management*

1. Introduction

Uric acid is predominantly formed by the enzymatic breakdown of nucleic acids and other purine-like substances from cellular metabolism as well as purines from diet. In recent years, it has been established that SUA is connected with the development of a range of illnesses. However, the mechanism is not clear. Existing studies believe that the dual role of uric acid in the oxidative process of the human body is the main mechanism involved in the development of various diseases. On the one hand, uric acid can promote the oxidative process in the human body by reducing the production of nitric oxide, activating the renin-angiotensin system and activating the chronic inflammatory response, which can lead to an increased risk of various diseases including cardiovascular diseases, and on the other hand, urea can reduce the risk of neurodegenerative diseases by scavenging oxygen free radicals and inhibiting protein and lipid peroxidation[1].

2. The Relationship Between Uric Acid and Cardiovascular Disease

2.1. SUA as a Risk Factor for Hypertension

A number of studies have demonstrated that those with greater uric acid levels are at increased risk of hypertension[2-6]. These investigations, which categorized patients according to uric acid levels, yielded consistent findings, although the particular group values differed; this association has also been verified in certain animal models[7, 8].

SUA is highly related to illness prognosis. A meta-analysis of seven randomized controlled trials with a total of 503 participants examined the relationship between uric acid-lowering therapy and blood pressure, which found that either inhibiting uric acid production or accelerating uric acid excretion could alleviate the elevation of blood pressure and even lower systolic blood pressure[9].

The current mainstream view is that the effect of SUA on blood pressure is divided into two stages: in the early stage of SUA, through the activation of the renin-angiotensin system, inducing oxidative stress to reduce the level of nitric oxide damage to the endothelial function and other mechanisms to cause hypertension; with the progress of the disease process, renal damage is gradually obvious; in this stage of the SUA level, even if the reduction of hypertension may still be present for a long time[10],Because of this tiered function of SUA in the development of hypertension, serum uric acid monitoring and early therapy are critical.

2.2. SUA as a Risk Factor for Coronary Heart Disease

Elevated uric acid levels have long been recognized as a marker of coronary heart disease with little

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predictive impact, but in recent years various studies have revealed that hyperuricemia may raise the risk of coronary heart disease. A cross-sectional investigation indicated that individuals with coronary heart disease had higher SUA levels[11]. A similar conclusion was obtained in a prospective cohort research study, which demonstrated a positive dose-dependent connection between SUA levels and the incidence of coronary heart disease, with a 14% rise in the risk of coronary heart disease when uric acid levels climbed by 100 umol/l[12] .

In terms of the prognosis of the disease: A large prospective study found a non-linear relationship between SUA levels and all-cause mortality from coronary heart disease, with a negative correlation between all-cause mortality from coronary heart disease and SUA when SUA was less than 345 umol/l and a positive correlation between all-cause mortality from coronary heart disease and SUA when SUA was greater than 345 umol/l[13]. In another large Asian cohort study, patients with coronary heart disease were divided into 3 groups (0-1, 2-3, 4) by the number of traditional cardiovascular risk factors in order to exclude the effect of traditional risk factors, and it was found that the risk of adverse cardiovascular events was significantly higher in patients with high uric acid levels than in patients with low levels of uric acid in the overall population, whereas in subgroups this difference was only observed in the group with 0-1 cardiovascular risk factor[14].Groups with no or fewer traditional cardiovascular risk factors are not treated seriously; however, the study indicated that elevated uric acid levels in this group were connected with cardiovascular events, underscoring the necessity of uric acid monitoring and early intervention.

In terms of disease mechanisms: firstly, SUA is connected with a variety of coronary heart disease risk factors, and secondly, SUA promotes oxidative stress to diminish nitric oxide levels, thus causing endothelial damage[15].

2.3. Relationship to Arrhythmia

A retrospective study in a diabetic population found that hyperuricemia was associated with heart conduction defects, and a multifactorial logistic regression model that included age, gender, and hypertension found that for every 1.81 mg/dl increase in SUA, the risk of heart conduction defects increased by 20%[16]. LiN et al. explored the relationship between different trajectories of uric acid changes and the development of heart block over a 6-year period and found that a high and stable trajectory of uric acid is associated with an increased risk of heart block, which provides a theoretical basis for monitoring uric acid levels [17].

Numerous investigations have demonstrated uric acid to be an independent risk factor for atrial fibrillation. The association was further studied in a meta-analysis which revealed a substantial linear relationship between SUA and the incidence of AF, with a 21% increase in AF risk for every 1 mg/dl rise in SUA[18].On the other hand, uric acid levels were associated with postoperative Prognosis of AF surgery, and a meta-analysis of 2,046 patients found that patients in the high uric acid group had a significantly higher rate of postoperative recurrence than those in the low uric acid group (OR = 2.21 [1.73, 2.83], $p < 0.001$)[19].

2.4. SUA as a Risk Factor for Heart Failure

The causal association between uric acid and congestive heart failure was studied in a Mendelian study, which indicated that elevated SUA caused an increased risk of heart failure [20] . The risk of hyperuricemia and heart failure and subsequent prognosis was reviewed in another study, which indicated that individuals with hyperuricemia had a considerably raised risk of heart failure and eventual all-cause mortality [21] .

3. Uric Acid and Neurological Disorders

3.1. Relationship to Different Types of Stroke

Previous research has revealed that elevated SUA levels are associated with an increased risk of ischemic stroke[22-24].A prospective study further investigated the relationship between dynamic changes in uric acid and ischemic stroke and ultimately found that stroke was associated with persistently high uric acid levels and that once uric acid levels reached a threshold, lowering uric acid levels at a later stage did not completely eliminate the risk of stroke that accumulated early due to high uric acid levels[25].On the other hand, however, the association between SUA and the prognosis of

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ischemic stroke is equivocal,Some studies have indicated that elevated SUA levels are advantageous in reducing the incidence of adverse events in ischemic stroke[26],whereas others have determined that there is no association between SUA levels and prognosis of ischemic stroke[27].In addition to this, a prospective study presents a new way of thinking, which indicated that the prognosis of ischemic stroke was better in non-hyperuricemia individuals with high SUA levels, but the prognosis for ischemic stroke in patients with hyperuricemia was worse[28] .

There are fewer studies on the relationship between uric acid and hemorrhagic stroke, and a meta-analysis showed no significant association between uric acid levels and hemorrhagic stroke[29]. Similar results were reported in a study evaluating the association between Black Africans and hemorrhagic stroke, a prospective cohort analysis that identified no significant correlation between hyperuricemia and prognosis in hemorrhagic stroke [30].

3.2. SUA as a Protective Factor in Parkinson's Disease

Previous studies have largely found that uric acid is a protective factor for Parkinson's disease and that lower uric acid levels associated with increased risk of Parkinson's disease[31-33].A meta-analysis that comprised 18 research studies similarly verified the preventive impact of high uric acid against Parkinson's disease, and it also indicated that the protective effect of high uric acid was substantial in a group of men under 60 years of age [34].Another meta-analysis comprised multiple papers from Europe, Asia, and North America, which indicated that uric acid levels were related to dementia in Parkinson's disease[35].In addition to this, uric acid levels have been associated with motor symptoms in Parkinson's disease, and a Brazilian study found that Parkinson's patients with low uric acid levels were more likely to have dyskinesia, which appears to be due to oxidative damage in the nigrostriatum exacerbated by low uric acid levels[36]. Previous studies have found large gender differences in the progression of Parkinson's disease, and an international multicenter study further examined the relationship between motor symptoms and gender and uric acid levels, finding that female patients with predominantly right-sided motor symptoms had lower uric acid levels, while there was no significant difference in male patients[37].

SUA can reduce the damage to neuronal cells caused by oxidative stress, which is currently the mainstream view. However, one study evaluated the association between antioxidant capacity and SUA in blood and cerebrospinal fluid, respectively, which indicated that cerebrospinal fluid antioxidant capacity did not substantially correlate with SUA level [38].This study suggests that the protective effect of SUA on Parkinson's disease still has unknown mechanisms.

3.3. SUA as a Protective Factor for Alzheimer's Disease

A meta-analysis studying revealed that low uric acid is a risk factor for Alzheimer's disease and Parkinson's disease and determined that this threshold is 292 umol/l[39].Although multiple studies have revealed a protective benefit of high uric acid against Alzheimer's disease, the mechanism remains unclear, and a recent low-animal study seems to offer a fresh explanation. In this study, a mouse model of Alzheimer's disease was established, and it was demonstrated that uric acid can improve cognitive function by activating the transcription factor EB, which leads to the enhancement of autophagy in microglial cells, further leading to the degradation of β-amyloid and finally improving cognitive function in mice[40].

4. Relationship Between Uric Acid and Other Common Diseases

4.1. SUA as a Risk Factor for Diabetes Mellitus

Several research studies in recent years have indicated an elevated risk of diabetes in those with elevated levels of uric acid[41, 42]; however, most of these studies ignored changes in uric acid in people with diabetes. A retrospective study in the United States spanning the years 1987-1998 indicated that those with elevated SUA levels were at increased risk for diabetes and that SUA levels reduced in patients diagnosed with diabetes during subsequent follow-up[43].The mechanism is unclear; however, one study has connected high uric acid levels to insulin resistance, which can lead to diabetes, and the same study found no link between high uric acid and impaired pancreatic beta cell function[44].

A prospective study indicated that persons with SUA levels were at greater risk of DPN, and the best SUA concentration for predicting the occurrence of DPN was 324 μmol/[45].However, several

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investigations have obtained the opposite conclusion, and a meta-analysis of 12 studies showed that hyperuricemia was related to an increased risk of DPN[46].This contradiction may be attributed to many confounding factors in clinical instances; consequently, Mendelian randomization experiments were done to study this relationship and eventually revealed a causal relationship between raised SUA and increased risk of diabetic neuropathy[47].A meta-analysis was undertaken to investigate the relationship between SUA and diabetic retinopathy, and it was discovered that SUA levels were linked with the risk of diabetic retinopathy[48].An analysis of 25 papers was undertaken to analyze the association between SUA and diabetic nephropathy, and it was revealed that there was a linear relationship between UA levels and the risk of diabetic nephropathy, with a 2% increase in risk for every 1 mg/dL increase in SUA[49].

It has been proposed that SUA may raise the risk of diabetes by causing insulin resistance; however, the exact pathophysiological mechanism remains unknown[50].The particular pathophysiologic process is not established. An animal study provides a feasible idea, which found that high SUA can cause increased levels of reactive oxygen species on the one hand, leading to a decrease in insulin secretion from pancreatic β-cells, and on the other hand, high SUA can inhibit glucose uptake, which can lead to insulin resistance[51].

4.2. SUA as a Risk Factor for Renal Insufficiency

A 4-year longitudinal study in China examined the relationship between changes in serum uric acid and kidney function, finding that for every 1/d increase in serum uric acid, the risk of kidney function decline increased by 14%, and restricted cubic spline analysis found that the risk of kidney function was significant when serum uric acid > 5 mg/dl [52]; In addition, two Japanese studies further examined the relationship between dynamic changes in serumic acid and changes in kidney function, both studies showed a significant negative correlation between changes in serum uric acid levels and kidney function [53, 54].

Previous research has indicated the following probable mechanisms: First, serum uric acid triggers the renin-angiotensin system, leading to increased glomerular and renal microvascular pressure, resulting in direct fibrosis of renal tissue; second, thickening of the preglomerular arteries and macrophage infiltration contribute to ischemia in the postglomerular circulation, ultimately worsening renal damage.[55].

4.3. SUA as a Protective Factor for Reduced Bone Density

Some investigations have indicated a beneficial correlation between serum uric acid levels and bone mineral density[56-58]. A meta-analysis of 19 studies from Asia, Europe, America, and Oceania likewise assessed the link between serum uric acid and BMD and similarly found a favorable correlation between higher serum uric acid levels and BMD[59].However, another cross-sectional survey indicated that the effect of serum uric acid on B is concentration-dependent, with a favorable relationship between serum uric acid and BMD when the uric acid level is <296 umol/l, but this relationship no longer exists when the uric acid level is further increased[60].A study in the United States further investigated the relationship between SUA and BMD, including animal experiments and a large cohort; however, the study found that chronic mild hyperuricemia in rats does not affect BMD, and the cohort study also did not find an association between serum uric acid and BMD after adjusting for confounding variables[61].

4.4. Positive Correlation Between Hyperuricemia and NAFLD

Several investigations have revealed a link between high serum uric acid and NAFLD[62, 63].A meta-analysis of 5,553 persons studying the association between serum uric acid and NAFLD supported the hypothesis that hyperuricemia can increase the risk of NAFLD and that this relationship may be independent of age, sex, and obesity [64].Meanwhile, some investigations have demonstrated that elevated uric acid levels in NAFLD patients may be related to more severe metabolic disease and higher mortality [65, 66].

Recent animal investigations have established that blood uric acid enhances hepatic fat accumulation by activating the ROS/JNK/AP-1 pathway, leading to liver [67].Additionally, Wan observed in animal models that serum uric acid triggers the NLRP3 inflammasome, resulting in fat cell formation and insulin resistance[68].

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5. Summary

As one of the primary antioxidants in the body, uric acid plays a crucial role in human metabolism. Although current research has found that uric acid is associated with various diseases. However, there are still numerous gaps in the research around uric acid, one of which is the unclear exact mechanism of uric acid in illness development. On the other hand, the therapy of uric acid is now quite restricted, generally primarily focusing on the prevention and treatment of gout. The possible reasons are as follows: 1. Uric acid levels are a risk factor for many common diseases, such as coronary heart disease and stroke, but the threshold for uric acid elevation in different research is variable, and there is presently no clear standard. 2. Most studies now only explore the impact of blood uric acid on a single condition, which cannot address the care demands of people with numerous diseases. For example, elevated blood uric acid may increase the risk of cardiovascular illness, while elevated blood uric acid can lessen the risk and long prognosis of neurodegenerative diseases (such as Parkinson's disease and Alzheimer's disease). These kinds of difficulties are fairly prevalent; however, there is currently no study in this area, which leads clinical practitioners to sometimes give up on controlling patients' uric acid levels due to lack of proof.

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