

Uric Acid Plays a Key Role in Hypertension and its Long-term Risk

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Abstract. Hypertension is a chronic disease now prevalent in modern societies and is a separate heart failure threat. If leave unattended a lengthy amount duration, it may lead to long-term risks such as stroke or heart attack, kidney damage, osteoporosis, and even death. Human metabolism of purines results in uric acid, which may have a significant impact on the onset and subsequent risk of pressure. The connection that exists among uric acid and hypertension was found to be progressively observable in Mendelian randomization studies, but no further strong subsequent studies have been conducted as of 2021 to illustrate the relationship. Meta-analysis studies have shown a potential link between elevated uric acid levels and an increased risk of hypertension, However, there is still a need to investigate the potential benefits of uric acid-lowering medications in reducing the risk of hypertension. Previous studies involving large sample sizes have indicated a positive association between uric acid levels and the likelihood of developing hypertension, but there is some geographic variation in the studies and the conclusions are limited and difficult to generalize. Multiple studies have given possible mechanisms at the mechanistic level for uric acid triggering hypertension or long-term risk, but the evidence-based value is low, giving no strong proof in terms of its relevance and continuity. This paper summarizes the existing evidence in the above points, puts forward its own insights, and looks forward to the future direction of scientific research, with a view to providing some references for future researcht.

Keywords: Uric acid; hypertension; Mendelian randomization study; Meta-Analysis, mechanism.

1. Introduction

Uric acid (UA) is produced by Metabolism of purines and the sources are categorized as endogenous and exogenous. Since the body does not contain enzymes to metabolize uric acid, once uric acid accumulates in the body, metabolic diseases such as hyperuricemia will occur. People's impression of uric acid often stays in the gout, gout is high uric acid caused by sodium urate precipitation in the joints resulting in a series of symptoms such as inflammation of the joints, gout attacks of joint inflammation brought about by the immense pain undoubtedly. Furthermore, numerous studies have uncovered a multitude of comorbidities associated with hyperuricemia and gout, of which cardiovascular disease (CVD) is one category [1]. Epidemiologic surveys have shown that the number of people suffering from cardiovascular diseases in China in 2022 will be up to 330 million, of which 245 million will be hypertensive, and other research has indicated that the occurrence of high blood pressure in adults is approximately 27.5%. This shows that hypertension, as a common cardiovascular disease, requires urgent clinical attention.

In recent years, significant progress has been made in improving the knowledge, treatment, and the control of hypertension, respectively 51.6%, 45.8% and 16.8%, the overall rate is still at a low level [2]. Various previous studies have shown that increased urate within cells plays a crucial role in development of essential hypertension [3]. However, there is still ongoing debate regarding the causal link between hyperuricemia and cardiovascular disease, and there is no definitive study pointing out that uric acid plays a decisive role in one of the pathogenic mechanisms of cardiovascular disease. Existing studies have attempted to dissect the multiple effects of uric acid on hypertension, but the relationships have been found to be inextricably linked, and although evidence-based studies have

had significant success, the results have not been obvious at the micro-mechanism level. Research progress stays in uric acid does have an impact on cardiovascular disease, but the research results of the impact of the specific mechanism is too scattered, clinical trials results of the mechanism of inference only stays in the speculation.

This paper summarizes the studies on the association between uric acid and the hypertension and its long-term risk from the level of mendelian randomization studies, meta-analyses and other large-sample size studies, summarizes the possible mechanisms of influence, and provides its own insights, with the aim of making certain outlooks on the future direction of scientific research or providing certain references for future studies.

2. Hypertension

According to the 2023 Chinese Guidelines for the Prevention and Control of Hypertension, hypertension in China is diagnosed based on systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg [2].

There are two main types of the hypertension: primary hypertension(also known as the essential hypertension) and the secondary hypertension is an independent systemic disease mainly manifested by elevated arterial pressure, and is the most common cardiovascular disease in China, accounting for about 95% of patients with hypertension; secondary hypertension refers to the elevation of blood pressure when suffering from certain diseases, such as chronic glomerulonephritis, renal artery stenosis, and renal pyelonephritis, also known as renal vascular hypertension, which accounts for about 5%-10% of patients with hypertension [4].

3. Mendelian randomization Study

Mendelian randomization study relies on the premise of association. (SNPs are strongly correlated with exposure factors), independence (SNPs are independent of confounders), and exclusivity (SNPs can only have an effect on the outcome through the exposure factor), and the effect of genetic variants that strongly correlate with exposure factors on results was observed to determine the causal relationship between exposure factors and study results.it is necessary to identify genetic variants that exhibit a strong correlation with the exposure factor.

3.1. Specific Research Description

A 2017 Mendelian randomization study, total of 107 Mendelian randomization studies were conducted analyses from 36 publications and performed a meta-analysis, ultimately concluding that gout-only outcomes were based on the compelling evidence ($P=3.55E-40$, $n=71,501$, efficacy $>99\%$) but that there was little credibility for a causal relationship between the two [5].

In 2019, a Mendelian randomization, a biobank consisting of 339,256 white British individuals (157,146 men and 182,110 women) from the UK was utilized. 31 genetic variants that associated with urate were selected as SNPs from a GWAS (genome-wide association study) to calculate to obtain a genetic risk score with a mean value of 0.44 (equivalent to a serum urate level of 0.44 mg/dL). The selected data were associated with the constructed model, replicated in the MR database, and sensitivity analyses were performed finally concluding that there is a strong association between urate and many diseases, such as the gout, the heart disease, the lipid metabolism disorders and so on, but the causal role of urate is supported only in gout, suggesting that the association between the urate and the CVD may due to the genetic variants, that is to say ,there is a strong association but causality is unknown [6].

In a recent study conducted in 2020, researchers used Mendelian randomization and genome-wide association analysis with the PLINK software to examine the relationship between urate and the blood pressure in a large sample of individuals of the European ancestry (n European descent=110,347, n White British =343,836). The findings showed that the elevated serum urate levels are associated

with the increasing systolic blood pressure (SBP) and may also have an impact on cardiovascular disease (CVD) risk. However, the researchers emphasized the need for high-quality clinical trials to determine the specific circumstances in which reducing urate levels could be beneficial for cardiovascular health [7].

3.2. Summary

The causal relationship is gradually observable as time advances, and the incomplete judgment of the former may be a slight error in the assumption of independence (there are too many confounders, and a more refined data analysis is needed) and the assumption of exclusivity (the selected SNPs are still somewhat associated with the outcome), but there is no more strong subsequent study to illustrate the relationship. Therefore, it is hoped that future studies can advance the research progress by increasing the amount of data, optimizing the data quality, updating the analysis method, and improving the precision of the validation analysis.

4. Meta Analysis

Meta-analysis is to use statistical concepts and methods to collect and organize empirical studies done by previous research for a certain topic, and to carry out research on the relationship of several factors.

4.1. Specific Research Description

A 2021 Meta-analysis study on the directness of uric acid and hypertension identified a total of 1,165 potentially relevant citations through literature search, and after deleting 419 duplicates, 698 weak correlations, and 37 studies that fell below the inclusion criteria, finally, 11 studies were included. The outcome revealed a significant correlation between high UA levels and increased risk of cardiovascular, the all-cause mortality, coronary artery disease (CAD), and major adverse cardiovascular events (MACE) in hypertensive patients. Specifically, the combined risk ratios (HR) were 1.51 for all-cause mortality, 1.68 for cardiovascular mortality, 1.31 for CAD, and 1.48 for MACE [8].

2022 A Meta-analysis, selected direct studies on uric acid and hypertension, finalized with the inclusion of 17 articles (79,358 subjects and 34,591 cases of prehypertension). In conclusion, it was found that higher levels of SUA were linked to a 46% higher risk of prehypertension compared to lower levels (RR 1.46, 95% CI 1.28-1.66). Additionally, SUA levels increased by 1 mg/dL, there was a 12% increased risk of prehypertension (RR 1.12, 1.08-1.17). This study further supports the idea that elevated SUA levels may be connected to a greater risk of prehypertension [9].

A 2020 Meta-analysis of studies on the directness of UA and the hypertension and further UA-lowering treatments (e.g., xanthine oxidase inhibitors (XOI, uric acid-lowering medications, including febuxostat and allopurinol)) in a comprehensive study of 6746 articles (3733 in Pubmed, Embase, and Cochrane, and 3013 in Wanfang, CQVIP, and CNKI). The study finally included 7 prospective cohort studies and 17 randomized controlled trials, with a total of 2768 duplicated citations, 3890 low relevance citations, and 64 citations that did not meet the inclusion criteria. Subgroup analyses showed that hyperuricemia increases the risk of hypertension, and that xanthine oxidase inhibitors (XOI) may help reduce the occurrence of MACE and overall cardiovascular disease events. CV safety was similar between allopurinol and febuxostat. However, febuxostat resulted in higher all-cause and cardiovascular mortality than allopurinol [10].

4.2. Summary

The relationship between elevated UA levels and the hypertension has been discussed by [8] and [9]. They suggest that there may be a connection between high UA levels and a higher incidence of hypertension. However, this conclusion is based on a study with limitations and is not backed up by larger data sets, and more longitudinal and intervention studies are needed to elucidate the

experimental conclusions. However, overall, this direction is promising. At the same time, [10] (published in 2020) has added a new assessment of the risk of CVD from UA-lowering therapy, and it has been suggested that the UA-lowering medications (e.g., xanthine oxidase inhibitors) may reduce the risk of hypertension, and this author is only venturing his own speculation based on the results of the study. In one study published in 2022, it was found that daily treatment with 600 mg of allopurinol did not lead to improve the cardiovascular outcomes in ischemic heart disease patients [11]. This raises questions about the effectiveness of UA-lowering drugs in managing hypertension. Due to the side effects, the potential negative impact of these drugs on hypertension risk could not be avoided. However, in future studies, if UA-lowering drugs are found to have a positive effect on reducing the risk of hypertension, it may further explain the close association.

5. Large Sample Size Studies

Large sample size study is stable and reliable, can better reveal the characteristics and laws of the overall, so that the statistical results are more representative and improve the effectiveness of the test.

5.1. Randomized controlled trial (RCT)

A RCT was conducted in a community in Xuzhou, Jiangsu Province (n=1198). All participants did not suffer from hypertension and were divided into four groups according to the UA level: Q1 group (206 cases): men's uric acid $\leq 302.8 \mu\text{mol/L}$, and women's $\leq 219.6 \mu\text{mol/L}$; Q2 group (209 cases): men's uric acid $\leq 302.9\sim 345.6 \mu\text{mol/L}$; Q2 group (209 cases): men's uric acid $\leq 302.9\sim 345.6 \mu\text{mol/L}$; Q2 group (209 cases): men's uric acid: $302.9\sim 345.2 \mu\text{mol/L}$, female uric acid: $219.7\sim 254.2 \mu\text{mol/L}$; Q3 group (205 cases): male uric acid: $345.3\sim 390.4 \mu\text{mol/L}$, female uric acid: $254.3\sim 291.7 \mu\text{mol/L}$; Q4 group (206 cases): male uric acid $\geq 390.5 \mu\text{mol/L}$, female uric acid $\geq 291.8 \mu\text{mol/L}$. 291.8 $\mu\text{mol/L}$ for women); the association between uric acid levels and hypertension was observed over 6 years of follow-up. The results showed that, in addition to age and fasting blood glucose, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low density lipoprotein, glutamine transpeptidase and creatinine all increased with the increase of uric acid. During the 6 years of follow-up, there was no trend of morbidity in the four groups except the first and second years. In the remaining 4 years, the cumulative incidence of hypertension increased with the increase of uric acid level, suggesting that UA is an independent risk factor. However, because the included population was only in one region, the interpretation of the results of the study may have limitations and may not be sufficient to generalize to the development of prevention and treatment strategies for hypertension in China [12].

In another randomized controlled trial, data were used from selected populations in six regions of Hunan province, 1538 hypertensive patients were selected, of which 85.24% were H-type hypertension, the researchers divided the study participants into four groups based on their UA levels, which were group A (n=385): $216 \mu\text{mol/L}$; Group B (n=384): $283 \mu\text{mol/L}$; Group C (n=385): $343 \mu\text{mol/L}$; and Group D (n=384): $429 \mu\text{mol/L}$. Using Group A as the control group, after adjusting the factors of age, gender and soon, the risk of HHT was increased in Groups B, C, and D by 17%, 61.1%, and 144.3%, respectively, compared with Group A. Logistic regression analysis showed that the ORs of UA and HHT in groups B, C, and D were 0.833, 1.935, and 2.516, respectively, compared with group A, suggesting that UA was associated with HHT within a certain level range. Therefore, maintaining a normal uric acid level in the clinic can help in the early prevention of hypertension. [13]

5.2. Cross-sectional Study

A cross-sectional study method was used to select 116,553 study subjects who underwent physical examination at Tongji Hospital affiliated with Huazhong University of Science and Technology, in which the detection rate of hyperuricemia was 26.1% and the detection rate of hypertension was 23.3%. They were divided into two groups, with 86,092 in the group without hyperuricemia, 30,461

participants in the hyperuricemia group. After adjusting for each confounding factor, hyperuricemia was found to be positively correlated with blood pressure values (OR=1.32, 95%CI 1.27,1.37, $P<0.001$). This is a good indication that health management of hypertensive people by controlling hyperuricemia is a direction worth exploring with greater feasibility [14].

5.3. Summary

Large sample size studies in different regions illustrate that as the level of UA increases, the incidence of developing hypertension or H-type hypertension also increases, proving the association between the two. However, there are some geographical variations in the studies. In addition, no good conclusions or opinions can be drawn about whether there are gender differences between UA and hypertension, or whether it is affected by time. However, it is indisputable that the management of uric acid should be paid attention to in hypertensive patients or those with risk factors for hypertension, and also the large sample size study should expand the regional scope to reduce the random error.

6. Mechanisms

6.1. Influence on Oxidative Stress

Xanthine oxidase acts as an enzyme in the UA synthesis pathway and is a generator of superoxide and hydrogen peroxide. Elevated levels of uric acid increase the by-products of xanthine oxidase and enhance the level of intracellular oxidative stress. Furthermore, the presence of uric acid not only decreases the levels of nitric oxide (NO) in the endothelial cells but also activates peroxynitrite-mediated lipid oxidation, leading to the stimulation of additional pro-inflammatory biomarkers [15]. Excessive oxidative stress contributes to the production of superoxide, which oxidizes BH_4 (tetrahydrobiopterin, a cofactor of NOS (a subunit of NO)) to BH_2 (tetrahydrobiopterin), which contributes to the uncoupling of NOS, leading to a decrease in NO production, an increase in O_2^- generation as well as the formation of unstable and reactive ONOOs; The lifespan of superoxide is extremely brief, allowing it to swiftly interact with NO to create OONOO- or rapidly transform into H_2O_2 . Extensive research conducted on animals and cultured cells has provided compelling evidence for a significant causal connection between reactive oxygen species (ROS) and hypertension. [16]

6.2. RAAS (renin-angiotensin-aldosterone system) is Overactivated

The liver is responsible for producing angiotensinogen in the RAAS. This, along with other peptides, plays a crucial role in regulating vasoconstriction. Through a series of enzymatic reactions, angiotensinogen is converted into angiotensin II (Ang II), which activates the Ang II type 1 receptor (AT1R). This activation leads to various physiological and pathophysiological effects, such as vasoconstriction and the sodium/water retention, ultimately impacting vascular function, such as promoting vasoconstriction and enhancing Na ion uptake, thereby causing hypertension [17]. In a clinical study in 2021, 233 subjects (116 males and 117 females) with AF were enrolled and then categorized into control and study groups based on whether they were currently using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor antagonists (ARBs). The data were recorded for one year, and the results showed that elevated uric acid may lead to over-activation of RAAS and aggravate oxidative stress [18]. UA may lead to hypertension by over activating the RAAS system. However, the sample was small and the patients are with AF, and other interfering factors were also more unrepresentative. It is hoped that future studies will fill the gap in this area.

6.3. Others

Some of the data also proved that uric acid itself has a certain solubility in the plasma, can increase plasma concentration and thus affect hypertension, but the degree of influence is too small; uric acid may also affect nerve excitation, vascular resistance and other aspects to affect hypertension, but ultimately associated with oxidative stress (nerve excitation regulation of oxidative metabolism level)

and RAAS (vascular resistance affects vascular function), and does not have a high degree of confidence! The article is clearly effective in other ways. The molecular mechanism level is the most complex, not only need to show the correlation of the step-by-step effect from uric acid to hypertension, but also need to prove the positive continuity of the process (e.g., it is indeed the uric acid-generated ROS that affects hypertension, not the interfering substances generated by other influences), and in the future we hope to increase the number of relevant clinical trials that explore the mechanism level to prove its relevance.

7. Conclusion

The strong correlation between UA and hypertension has been reasonably proved in Meta-analysis, RCTs, cross-sectional studies, etc., but the causal relationship still needs further research to clarify, in which Mendelian randomization research from the genetic level and mechanism research from the molecular mechanism level are a great impetus for the future advancement in this field. In the future, we can expand the sample size, change the experimental entry point, update the experimental method, and add validation experiments to enhance the precision and credibility of the experiments. Meanwhile, although the strong correlation has been elucidated, the various aspects of its interactions can be further explored, which may be used as new evidence to verify the correlation.

Regardless, the present research adequately warns individuals with hypertension about their uric acid levels. Considering the potential effect of elevated UA levels on long-term likelihood of developing hypertension, future clinical nutritional therapy should prioritize the consumption of a low-purine diet alongside a balanced diet to prevent and treat hypertension.

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