Review

Serum Uric Acid: A Risk Signal and a Treatment Target for Essential Hypertension

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Uric acid is the end product of purine metabolism in humans. During the past several decades, lifestyle and dietary changes and the aging of overall population contribute to progressively rising of serum uric acid levels. Although a number of epidemiologic data has suggested that elevated serum uric acid levels are associated with increased risk for hypertension and cardiovascular diseases, the causal role of uric acid in the development of hypertension is still inconclusive. In this review, we summarize experimental and population studies on uric acid and possible links to hypertension and the pathogenic mechanisms. We also discuss environmental factors and genetic variations that affect serum uric acid levels and disease risks.
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Key Words: *uric acid, hypertension, hyperuricemia*

INTRODUCTION

Uric acid is the end product of purine metabolism. Uricase, a hepatic enzyme present in most mammalian species, degrades uric acid to allantoin and thereby maintains uric acid at low levels in the blood (<2 mg/dl). The human beings lost uricase activity because of genetic mutants during the evolution, and hence have higher (>2 mg/dl) and less regulatable uric acid levels. During the past several decades, lifestyle and dietary pattern has changed resulting from economic prosperity, and life expectancy in the general population has greatly increased; there is evidence that serum uric acid levels are progressively rising over the same period in developed countries including United States[1,2] as well as developing countries such as China.[3]

The epidemiological link between hyperuricemia and gout was established more than 150 years ago. Elevated serum uric acid levels are also frequently observed in patients with hypertension and cardiovascular diseases. To explore whether these two observations be linked, a number of epidemiologic studies in various populations have suggested that hyperuricemia is an independent risk factor for hypertension and cardiovascular diseases.[4,5] However, since uric acid levels are highly correlated with renal function, obesity, and metabolic abnormalities, the question is that whether the link is an independent and even causal mechanism, or a consequence of disease, or simply as a surrogate marker. Thus, the relative importance of these associations remains controversial and is largely ignored in medical practices. Up to date, uric acid is considered an important, but not an essential risk factor for hypertension by either the American Heart Association[6] or the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.[7]

This review summarizes relevant studies on uric acid and possible links to hypertension and the pathogenic mechanisms. The mounting evidence promotes clinical trials to determine whether lowering serum uric acid levels would be of clinical benefit in the prevention or treatment of hypertension, especially among the youngsters with early-onset hypertension.

INCREASED RISK FOR ESSENTIAL HYPERTENSION IN HYPERURICEMIA

An elevated uric acid level is observed in 25%-60% of patients with untreated essential hypertension.[1] In the past 30 years, over 15 epidemiologic studies have reported that hyperuricemia contributes to an increased relative risk for hypertension development within five years, independent of other conventional cardiovascular risk factors, including obesity and renal function (**Table 1**). Studies of elevated uric acid levels and the development of hypertension have obtained consistent, continuous, and similar magnitudes, with the relative risks of 1.5-2.0.[8-22,24,25] Only one study showed that uric acid did not predict the development of hypertension, in which the involved subjects had developed hypertension after the age of 60 years old.[23] Most evidence was from Caucasian-based cohorts; a large community-based prospective study comprising 7,220 participants (mean age 37 years; 73.8% men) in the Qingdao Port Health Survey in China provided data for the first time that a positive association was also observed between uric acid and incidence of hypertension during four years follow-up in the Chinese population. In addition, a combined high uric acid

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concentrations and abdominal obesity was associated with higher risk (3.0-fold in men and 3.4-fold in women) of incident hypertension than their individual effects.

Hyperuricemia is also common among adults with prehypertension and promotes blood progression from prehypertension to hypertension.[19,26] These observations that hyperuricemia precedes the development of hypertension indicates that it is not simply a result of hypertension. Hyperuricemia is more common in primary hypertension than in secondary hypertension, and this association is stronger in adolescents. Hyperuricemia (>5.5 mg/dl [330 μmol/L]) was observed in nearly 90% of adolescents with early-onset essential hypertension, while uric acid level was significantly lower in controls and teens with secondary hypertension.[27] Data from the Framingham Heart study showed that the strength of the association between serum uric acid and hypertension decreases with increased patient age and duration of hypertension,[28] suggesting that uric acid may play an important role in younger subjects with early-onset hypertension.

Table 1. Elevated serum uric acid levels and relative risk of hypertension.

Author	Year published	Country	Study	No. of Participants	Follow-up, years	Relative risk (95% CI) of hypertension
Kahn et al[8]	1972	Israel	Israel ischemic heart disease study	10000 men	5	1.8 (1.30-2.53) (uric acid ≧5.0 mg/dl)
Selby et al[9]	1990	US	Kaiser Permaente	2062 adults	6	2.1 (1.20-3.98) (high vs. Low quintile of uric acid)
Hunt et al[10]	1991	US	University of Utah	1482 adults	7	1.44 (1.03-2.01) (per SD increment in uric acid)
Jossa et al[11]	1994	Italy	Olivetti Heart	619 men	12	1.23 (1.07-1.39) (per 1.0 mg/dl increase in uric acid)
Dyer et al[12]	1999	US	CARDIA study	5115 men	10	1.21 (1.03-1.41) (per SD increment in uric acid)
Taniguchi et al[13]	2001	Japan	Osaka Health Survey	6356 men	10	2.0 (1.56-2.60) (high vs. Low quintile of uric acid)
Imazu et al[14]	2001	US/Japan	Hawaii–Los Angeles–Hiroshima Study	140 men	15	2.0 (1.02-3.9) (high vs. Low quartile of uric acid)
Masuo et al[15]	2003	Japan	Osaka Factory	433 men	5	Increased 27 mmHg systolic blood pressure (per1.0 mg/dl increase in uric acid)
Nakanishi et al[16]	2003	Japan	Osaka Health Survey	2310 men	6	1.13 (1.06-1.21) (per SD increment in uric acid)
Nagahama et al[17]	2004	Japan	Okinawa	4489 adults	23	1.46 (1.09-2.03) in men (uric acid ≧7 mg/dl) 1.94 (1.05-3.57) in women
Alper et al [18]	2005	US	Bogalusa Heart Study	679 children	11	Increased risk for diastolic hypertension
Sundström et al[19]	2005	US	Framingham Heart study	3329 adults	4	1.17 (1.02-1.33) (per SD increment in uric acid)
Perlstein et al [20]	2006	US	Normative Aging Study	2062 men	21	1.25 (1.08-1.34) (uric acid ≧6.5 mg/dl)
Mellen et al [21]	2006	US	ARIC study	9104 adults	9	1.1 (1.02-1.14) 1.2 (per SD increment in uric acid)
Shankar et al [22]	2006	US	Beaver Dam Health Survey	2520 adults	10	1.65 (1.41-1.93) (high vs. Low quintile of uric acid)
Forman et al [23]	2007	US	Health Professionals' Follow-up	750 men	8	1.02 (0.92-1.13) (per SD increment in uric acid)
Krishnan et al [24]	2007	US	MRFIT study	3073 men	6	1.10 (1.02-1.19) (per SD increment in uric acid)
Forman et al [25]	2009	US	Nurses' Health Study	1496 women	8	1.89 (1.26-2.82) (high vs. Low quintile of uric acid)
Zhang et al [26]	2009	China	Qingdao Port Health Survey	7220 adults	4	1.39 (1.16-1.68) in men 1.85 (1.06-3.24) in women (high vs. Low quartile of uric acid)

Preliminary clinical trial data provides robust evidence for uric acid in early-onset primary hypertension. In a double-blind, placebo-controlled cross-over trial of 30 hyperuricemic adolescents with essential hypertension, lowering uric acid levels with the xanthine oxidase inhibitor allopurinol was associated with a significant decrease in both casual (measured at the physician's office) and ambulatory blood pressure over a 4-week period.[29] For patients in whom uric acid levels decreased to <5 mg/dl (300 μmol/L), blood pressure became normal in 86% (19 of 22 patients), compared to 3% (1 of 30) during the placebo phase of the study. These data support the etiological role of uric acid in hypertension in this specific adolescent population, but it remains unknown whether these findings would be applicable to adult populations who afford the much larger burdens of hypertension disease.

Then, if hyperuricemia is an etiological factor in hypertension, what are the mechanisms, and will its modification affect outcome?

Table 2. Genetic locus and variants associated with serum uric acid levels identified in recent whole-genome association studies.

Locus	Chromosome	SNP	Allele associated with uric acid level	Population	SNP function	Gene annotation	Refs
Chr 1 centromere	1	Chr1_142697422 T>C	C	Icelandic	undefined	Undefined	[43]
Nearby PDZK1	1q21	rs12129861 A>G	G	Icelandic, European	5' near gene	Enocding PDZ domain containing 1	[41,43]
GCKR	2p23	rs780094 C>T	T	Icelandic, European	Intronic SNP	Encoding glucokinase regulatory protein	[41,43]
SLC2A9	4p16.1	rs16890979 C>T	C	American white, American black, Icelandic, European	Missense SNP, leading to a valine-to-isoleucine amino acid change at position 282 (V282I)	Encoding solute carrier family 2 (facilitated glucose transporter), member 9	[40, 41,43]
ABCG2	4q22	rs2231142 G/T	T	American white, American black, Icelandic, European	Missense SNP, leading to a glutamine-tolysine amino acid change at position 141 (Q141K)	Encoding the ATP-binding cassette subfamily G, member 2, which serves as urate efflux transporter	[40, 41,43]
LRRC16A	6p22.2	rs742132 G>A	A	European	Intronic SNP	Encoding leucine rich repeat containing 16A	[41]
RREB1	6p25	rs675209 C>T	T	Icelandic, European	5' near gene	Encoding ras responsive element binding protein 1	[41,43]
SLC17A1	6p23-p21.3	rs1165196 G>A	A	Icelandic, European	Missense SNP, leading to a threonine-to-isoleucine amino acid change at position 269 (T269I)	Encoding sodium-dependent phosphate transport protein 1	[41,43]
SLC17A3	6p21.3	rs1165205 A>T	A	American white, Icelandic,	Intronic SNP	Encoding solute carrier family 17 (sodium phosphate), member 3	[40,43]
SLC16A9	10q21.3	rs12356193 G>A	A	Icelandic, European	Intronic SNP	Encoding monocarboxylic acid transporter 9 (MCT9)	[41,43]
SLC22A11	11q13	rs2078267 T>C rs17300741 G>A	C A	Icelandic, European	Intronic SNP	Encoding solute carrier family 22 (organic anion/urate transporter), member 11	[41,43]
SLC22A12	11q13	rs505802 C>T	T	European	5' near gene	Encoding solute carrier family 22 (organic anion/urate transporter), member 12	[41]
INHBC	12q13.1	rs1106766 T>C	C	Icelandic	5' near gene	Encoding inhibin, beta C	[43]
ALDH16A1	1913.33	rs150414818 C>G	G	Icelandic	Missense SNP, leading to a proline-to-arginine amino acid change at position 527 (P527R)	Encoding aldehyde dehydrogenase (ALDH) 16 family, member A1, implicated in purine metabolism	[43]

PROPOSED MECHANISMS FOR URIC ACID-MEDIATED HYPERTENSION

In the late 1990s, Johnson and colleagues developed an experimental model using a pharmacologic inhibitor of urate oxidase, oxonic acid, which allowed the study of sustained mild hyperuricemia. These animal studies provided the first direct evidence that uric acid elevation may lead to blood pressure rise. In this model, after a 7-week treatment period with 2% oxonic acid in rat's standard diet, the uric acid level is increased and hypertension develops. The increase of blood pressure is linearly correlated with the rise of serum uric acid levels; and blood pressure decreased when uric acid

was reduced with either a xanthine oxidase inhibitor or a uricosuric agent.[30] Hyperuricemic and hypertensive rats showed the histological characteristics of microvascular renal disease with an expansion of the vascular smooth muscle and narrowing of the lumina of the afferent arterioles. This lesion is similar to arteriolosclerosis, the classic features of essential hypertension in humans. Further experimental results showed that microvascular changes still developed if uric acid was not lowered, even when blood pressure was normalized by a diuretic, indicating that uric acid may cause microvascular arteriolosclerosis independently of hypertension.

Similar microvascular lesions can be induced in rats with normal serum levels of uric acid through the infusion of angiotensin II or blockage of nitric oxide synthesis. Once these lesions are induced, a salt-sensitive hypertension develops and persists even when angiotensin II stimulus is stopped.[31] In mentioned above hyperuricemic rat model, when the uricase inhibitor was stopped after renal microvascular disease and interstitial inflammation had become pronounced, blood pressure would be controlled only if the rats remained on a low-salt diet.[30] Recent in vitro studies also have elucidated the possible mechanism of uric acid-mediated arteriosclerosis. For example, in experiments with cultured vascular smooth-muscle cells, uric acid induces cellular proliferation, inflammation, oxidative stress, and activation of the local renin–angiotensin system.[32,33] Kurra et al reported that the administration of an uricase inhibitor can improve endothelial function in the carotid.[34]

Both the experimental and human studies provide a possible rationale for how uric acid might cause hypertension in humans, and for why uric acid would be linked with newly diagnosed or early-onset hypertension, since longstanding hypertensive subjects might already have renal microvascular disease, and their current hypertensive condition may be due to an advanced and irreversible salt-sensitive damage.

ENVIRONMENTAL AND GENETIC FACTORS THAT INFLUENCE SERUM URIC ACID LEVELS

It is widely recognized that the increased prevalence of obesity has contributed to the increased prevalence of hypertension. Over the past 200 years fructose intake in the developed countries has increased significantly, which correlates temporally with increased prevalence level in hypertension and obesity.[35] Fructose may be uniquely unhealthy sugar because it rapidly causes depletion of ATP and raises uric acid levels. Experimental data support a link between fructose intake, hyperuricemia, and increases in blood pressure.[36] Excessive intake of other foods (purine-rich fatty meats) or drinks (such as beer), exposure to lead, or low birth weight may result in chronic hyperuricemia and thereafter increased the risk of hypertension.

Besides environmental factors, there is evidence that genetic factors involved in purine metabolism, renal function, or other highly correlated traits are associated with uric acid levels, with 40% estimated heritability.[37] Recently, genome-wide association (GWA) studies have identified associations with sequence variants at several loci (**Table 2**). Initially, single nucleotide polymorphisms (SNPs) in the SLC2A9 gene (solute carrier family 2, member 9 gene) were identified,[38,39] which were linked with low renal fractional excretion of uric acid. A missense SNP rs16890979 in SLC2A9 leads to valine-to-isoleucine aminoacid substitution (V253I) and has the strongest association with uric acid concentration and gout. Dehghan et al identified two new loci, ABCG2 and SLC17A3.[40] ABCG2 encodes a transporter of the ATP-binding cassette (ABC) family; a missense SNP in ABCG2 (rs2231142; Q141K) was associated with uric acid concentration and gout in both white and black individuals and may be a causal candidate variant.

A recent meta-analysis from 14 GWA studies totaling 28,141 participants of European descent identified 9 loci associated with serum uric acid concentrations at genome-wide significance level ($P<5 \times 10^{-8}$).[41] The novel loci included the glucokinase regulator protein (GCKR) of which the same SNP rs780094 has previously been observed a strong association with triglycerides, glucose and insulin levels.[42] Most recently, Sulem et al. identified a low-frequency missense variant (c.1580C>G) in the aldehyde dehydrogenase 16A1 (ALDH16A1) gene associated with gout and serum uric acid levels through whole-genome sequencing of 457 Icelanders.[43] For these risk loci, mediating mechanisms for elevated uric acid levels remains to be elucidated.

FURTHER PERSPECTIVES

Although a number of genetic variations are consistently proved to be associated with serum uric acid levels and increased risk of gout, sparse data is available on whether these variations are associated with the risk of hypertension incidence. Individual common genetic variants generally confer a modest effect size on the variation in serum uric acid concentration, and their combination may result in a large association with uric acid levels and disease risk. Abbas Dehghan and colleagues reported that a genetic risk score of high-risk alleles at the three urate transportation-related loci (rs16890979 C in SLC2A9, rs2231142 T in ABCG2, and rs1165205 A in SLC17A3) showed significantly higher serum uric acid concentration and gout risk compared to those with no risk alleles.[40] Knowledge of genotype could help to identify individuals at risk of developing hyperuricemia long before the onset of clinical features of the disease. Moreover, understanding mechanisms through which SNPs are associated with serum uric acid levels might help identify new targets for intervention.

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CONFLICT OF INTEREST

None.

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