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Serum Uric Acid as a Risk Marker for Metabolic Syndrome in Middle-Aged Adults

Katarzyna Jablonski¹●, Henrike Brockhaus²●, Duarte Magalhaes³●

¹Associate Professor, Department of Clinical Biochemistry, Kashubian Institute of Medical Sciences, Kartuzy, Poland.

²Senior Research Fellow, Department of Plant Biochemistry, Hunsrueck Institute of Biochemistry, Simmern, Germany.

³Research Associate, Department of Plant Biochemistry, Minho Valley Institute of Health Research, Viana do Castelo, Portugal.

Email: ¹k.jablonski@kims.edu.pl, ²h.brockhaus@hib-s.de, ³d.magalhaes@mvivr.pt

ORCID: ¹0000-0001-4909-1351, ²0000-0001-3022-5196, ³0000-0001-4524-0049

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ABSTRACT

Serum uric acid is measured in almost every routine biochemistry panel, and in adults of middle age it tends to run higher in people who also have central obesity, raised blood pressure, disturbed lipids and impaired glucose handling, the cluster called metabolic syndrome. Whether uric acid is a useful marker of that cluster, a contributor to it, or simply a bystander carried along by the same causes is still argued. This narrative review summarises published work on how urate is produced and excreted, how insulin resistance and diet shift it, the mechanisms proposed to link it to vascular and metabolic disease, and what cohort studies, genetic studies and treatment trials have and have not shown. Associations in cohorts are consistent, while studies that use genetic variants as instruments give little support to a causal effect on blood pressure or heart disease, and trials of urate lowering are few and small. The review argues that uric acid is best treated as a marker of risk whose causal role is unproven, describes the confounding that makes interpretation difficult, and lists the evidence that would settle the question. No new data are reported.

Keywords: Uric acid; Hyperuricaemia; Metabolic syndrome; Insulin resistance; Cardiometabolic risk; Biomarker; Narrative review

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Article Class: Narrative Review

1. Introduction

Uric acid is the end product of purine breakdown in humans, and it is one of the cheapest numbers on a routine biochemistry report. For most of the twentieth century it belonged to the rheumatologist, because very high concentrations lead to crystal deposition

and gout (1, 2). That picture has widened. Surveys of general populations show that raised urate is common, and that it travels with a long list of other conditions, among them hypertension, diabetes, kidney disease and obesity (3, 4).

Metabolic syndrome is the clustering of central obesity, raised blood pressure,



atherogenic lipid changes and disturbed glucose handling in one person. Definitions have been brought closer together without being made identical (5, 6). The syndrome is common (7), is associated with later cardiovascular disease (8), and its status as a distinct entity has been questioned (9).

It is no surprise that urate and metabolic syndrome have been studied together. Adults with raised urate are more likely to meet the criteria for the syndrome (10), and the pattern has been seen in young people too (11). What is less certain is its meaning: uric acid might mark the syndrome, help to cause it, or rise as a consequence. This review sets out the biology of urate, the proposed mechanisms, and the epidemiological, genetic and trial evidence for middle-aged adults. It reports no measurements of its own, and the title should not be read as describing a local study. The aim is a fair account of what has been shown, as against what has merely been repeated.

2. Literature Review

2.1 How the Body Handles Urate

Humans, unlike most mammals, lack a working uricase, so purine metabolism ends at uric acid. Urate in blood reflects a balance between production, from nucleotide breakdown and dietary purines, and elimination, mostly by the kidney. Identification of a urate–anion exchanger in the proximal tubule showed that transporters, not just filtration, set the blood concentration (12), and genome-wide studies have linked common variants in several transporter genes to serum urate and gout (13, 14).

Diet and body composition matter too. Purine-rich foods such as meat and seafood raise the risk of gout, whereas dairy protein appears protective (15). Beer and spirits are associated with higher urate

(16), as are sugar-sweetened drinks and fructose (17, 18, 19), a point that matters because fructose is central to one theory of metabolic syndrome. Table 1 lists these influences.

Table 1. Common influences on serum urate in middle-aged adults.

Influence	Direction	Source
Sugar-sweetened drinks and fructose	Raise	(17, 18, 19)
Purine-rich foods, mainly meat and seafood	Raise	(15)
Beer and spirits	Raise	(16)
Visceral fat accumulation	Raise	(20)
Weight loss with diet change	Lower	(21)
Common genetic variants in urate transporters	Raise or lower	(12, 13, 14)

Note: Directions are those reported in the cited surveys and cohorts; magnitudes are omitted because they differ by population.

2.2 Urate in the Metabolic Cluster

Large surveys find that the prevalence of metabolic syndrome climbs across increasing bands of serum urate (10), and the relation holds in young people (11). The cohorts differ in age, sex, body size and criteria, which makes it hard to say what a single threshold means.

The physiology runs in both directions. Insulin reduces renal excretion of urate, so people with insulin resistance and hyperinsulinaemia tend to show reduced clearance, one of the first explanations offered for the clustering (22, 23). In the other direction, visceral fat has been linked to overproduction of urate (20). A raised urate could therefore be a result of the metabolic state before it is anything else, as Figure 1 sketches. This is one reason the same marker can look decisive in one report and unremarkable in the next.

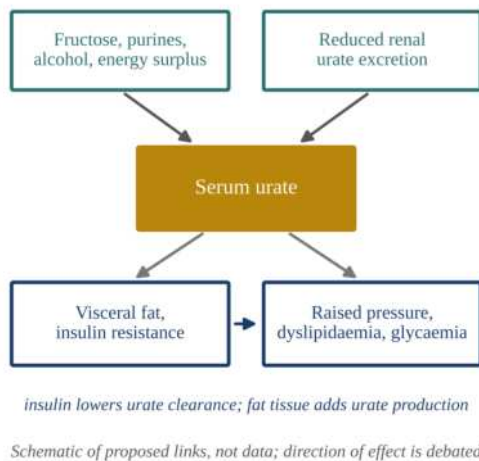


Figure 1. Proposed relations between urate, diet, the kidney and the features of metabolic syndrome (schematic, not data).

2.3 Proposed Mechanisms of Harm

Experimental work suggests that urate could be more than a passive marker. In rats, a high-fructose diet produced features of metabolic syndrome and lowering urate prevented some of them (24), and a broader synthesis argues that fructose-driven urate generation promotes fat accumulation and insulin resistance (25). In culture, urate caused oxidative stress in fat cells (26) and was linked with impaired endothelial function (27). Raised urate also lifted blood pressure in rats by a crystal-independent mechanism (28). Most of these findings come from animals or isolated cells, so they show what is possible rather than what happens in people. Table 2 collects the proposals and their weaknesses.

The picture has a complication. Urate is also a powerful antioxidant in plasma, and an early hypothesis held that it protected humans against oxidant damage (30). The same molecule can be protective outside cells and pro-oxidant inside them (31), so simple statements that urate is good or bad for vessels are unlikely to be right. That sounds like a small distinction, yet much of the argument turns on it.

Table 2. Mechanisms proposed to link raised urate with metabolic syndrome.

Proposed link	Type of evidence	Main caveat
Fructose raises urate and fat deposition	Animal work, feeding studies (24, 25)	Human relevance of doses debated
Urate injures the endothelium	Cell and animal work (27)	Intracellular and plasma urate differ
Urate stresses fat cells	Cell culture (26)	Not shown in people
Raised urate lifts blood pressure	Rat model; one small trial (28, 29)	Short follow-up, young patients
Insulin resistance lowers urate excretion	Physiological studies (22, 23)	Points the opposite way round

Note: Qualitative summary of the literature discussed in the text; the strength of evidence differs widely between rows.

2.4 Evidence from Cohorts, Genes and Trials

Prospective cohorts have found that higher urate predicts later hypertension (32), type 2 diabetes (33, 34) and coronary events (35). The associations are modest and in several analyses weaken once other risk factors are considered, and reviews have reached cautious conclusions about urate as a risk factor in its own right (36, 37).

Genetic studies offer a different test. If a person inherits variants that raise urate for life, and those variants are unrelated to the usual confounders, their link with disease reflects causal effects, provided other assumptions hold (38). A large analysis in two cohorts found that genetically higher plasma urate was not convincingly associated with ischaemic heart disease or blood pressure, although observational estimates had pointed that way (39). This does not rule out small effects, and it concerned heart disease and blood pressure more than the whole syndrome.



Treatment trials are the third source, and they are scarce. A small randomised trial in hypertensive adolescents found that allopurinol lowered blood pressure (29), and a trial in chronic kidney disease reported benefit for kidney progression and cardiovascular events (40). Neither tested middle-aged adults with metabolic syndrome (Figure 2). Absence of a finding in a small study is not evidence that nothing is there.

	Blood pressure	Diabetes	Heart disease
Cohort studies	associated	associated	associated
Mendelian randomisation	not supported	unclear	not supported
Treatment trials	small trial, positive	sparse	sparse

Qualitative reading of the literature in the text; schematic, not data

Figure 2. Qualitative reading of three kinds of evidence for three outcomes (schematic, not data).

3. Materials and Methods

3.1 Scope

The review asks whether serum uric acid in middle-aged adults is a marker of metabolic syndrome, a contributor to it, or both, and what would be needed to tell the difference.

3.2 Literature Assembly

We drew on peer-reviewed work in clinical biochemistry, epidemiology and genetics, chosen for relevance, influence and clarity of method. No formal systematic search was run and none is claimed; this is a narrative synthesis shaped by the authors' judgement, so effect estimates from individual studies are deliberately not quoted.

3.3 Appraisal Framework

To weigh the studies we asked four questions of each design. Was urate measured in a way that fits the question? Were adiposity, diet, alcohol and medication handled adequately? Was the direction of effect examined, for instance with genetic instruments or intervention? Were the conclusions proportionate to the design? Table 3 lists what each kind of study can and cannot show.

Table 3. Kinds of evidence on uric acid and cardiometabolic disease, and what each can show.

Design	Can show	Cannot show
Cross-sectional surveys	Co-occurrence at one time (4, 10)	Order of events
Prospective cohorts	Urate preceding disease (33, 41)	Freedom from confounding
Meta-analyses	Consistency across cohorts (32, 35)	Causation, if inputs are biased
Genetic instruments	Effect of lifelong urate difference (38, 39)	Effect of short-term lowering
Randomised trials	Effect of lowering urate (29, 40)	Long-term outcomes, when small

Note: Appraisal is the authors' qualitative reading of the design type, not a scoring of any individual study.

4. Results

4.1 What the Association Looks Like

Across surveys and cohorts the association is consistent in direction. Adults with metabolic syndrome have on average higher urate than those without (4, 10), and prospective studies, though not all, find that higher baseline urate precedes the syndrome, diabetes or hypertension (32, 33, 41). Meta-analysis supports a modest link with coronary disease (35).

The size of the association is harder to pin down. Estimates differ with the definition of the syndrome, sex, age and ethnic group, and the studies seldom agree on which feature carries the link; urate is also



related to insulin resistance in Asian adult populations (42). Because several components of the syndrome themselves raise urate, adjustment for all of them can remove most of what is left, and the investigator must decide whether that is control for confounding or for a mediator. Taken one at a time such differences look minor, but they add up across a population.

4.2 Confounding and Reverse Causation

Three kinds of distortion recur. The first is confounding by adiposity, diet and alcohol, all of which push urate up and are risk factors in their own right (16, 18, 20). The second is kidney function: reduced filtration raises urate and also raises cardiovascular risk, so the two can move together without a causal link (4, 36). The third is reverse causation, in which insulin resistance lowers urate excretion and so raises the number we measure (22). Association of this kind is a reason to look further, not a reason to act.

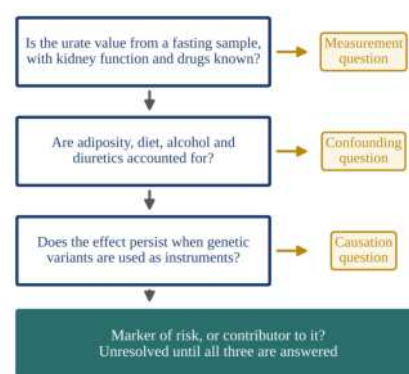
4.3 Does Lowering Urate Help?

If urate were a cause, lowering it should help. The adolescent allopurinol trial suggests that blood pressure can respond (29), but participants were young and the trial short; the kidney trial was open-label and selected by kidney disease (40). We found no adequately large randomised trial in middle-aged adults with metabolic syndrome among the sources reviewed.

The genetic data cut the other way. If lifelong exposure to higher urate does not raise heart disease or blood pressure (39), the cohort associations probably reflect shared causes. That inference has limits, since genetic instruments for urate are partly entangled with kidney and metabolic traits. A fair reading is that the causal case is unproven, not refuted.

Figure 3 turns the appraisal into three questions, and putting the strands together a defensible summary is brief. Urate is

reliably associated with the cluster, the associations probably reflect a large share of shared causes and reverse effects, a causal contribution has not been established and may be small, and treatment trials are too few to settle the matter. It is a modest claim, and it is the one the literature will currently bear.



Schematic of appraisal questions, not data

Figure 3. Three questions to ask before treating a raised urate as a cause (schematic, not data).

5. Discussion

5.1 Interpretation and Clinical Reading

For the laboratory and the clinician, the most useful position is that serum uric acid is a marker. It is cheap, reproducible and available, and a raised value should prompt attention to weight, diet, alcohol, kidney function and medication, along with the other components of the syndrome (5, 6). Reducing sugary drinks, alcohol and excess weight lowers urate and also improves the metabolic profile for reasons unrelated to urate (17, 19, 21), which makes causation harder to test than it first appears. The strongest reason for caution is the conflict between the cohort data and the weak genetic signal (39); treatment of asymptomatic hyperuricaemia lies outside this review (1, 2).

5.2 Limitations

This is a narrative review and shares the weaknesses of the form. Selection of



sources reflects judgement, no formal scoring of study quality was done, and numerical estimates are deliberately not reported; a reader who needs an effect size should consult the original papers. Reviews are more useful when they say where the evidence stops than when they smooth it over.

5.3 What Would Settle the Question

Three kinds of study would help most. First, large placebo-controlled trials of urate lowering in middle-aged adults with the syndrome and without gout, measuring blood pressure, glycaemia and vascular outcomes over several years. Second, genetic studies that use many more variants and try to separate urate from kidney and metabolic traits (14, 38). Third, long cohorts with repeated measures of urate, body composition and kidney function.

Until then, authors can improve reports by stating how urate was measured, which medicines participants took and how kidney function was handled. These cautions apply with equal force to many other biomarkers.

6. Conclusion

Serum uric acid is consistently higher in middle-aged adults who have the features of metabolic syndrome, and prospective studies suggest that it often rises before disease appears, which makes it a reasonable marker of cardiometabolic risk. The evidence that it contributes to the syndrome is weaker: mechanistic work is suggestive but far from human practice, genetic studies give little support to a causal effect on blood pressure or heart disease, and trials of urate lowering are few and small. A raised urate therefore calls for a look at the whole metabolic picture, not for a conclusion about urate itself.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

K.J. conceived the review and wrote the sections on clinical biochemistry and interpretation. H.B. wrote the sections on urate metabolism and mechanisms. D.M. wrote the sections on epidemiology and appraisal of study designs. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No human participants or animals were involved and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

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