Curr Rheumatol Rep (2017) 19: 60
DOI 10.1007/s11926-017-0688-y

Gout and Metabolic Syndrome: a Tangled Web

Gabrielle E. Thottam[1,2] · **Svetlana Krasnokutsky**[2,3] · **Michael H. Pillinger**[2,3]

Published online: 26 August 2017

Abstract
Purpose of review The complexity of gout continues to unravel with each new investigation. Gout sits at the intersection of multiple intrinsically complex processes, and its prevalence, impact on healthcare costs, and association with important co-morbidities make it increasingly relevant. The association between gout and type 2 diabetes, hypertension, hyperlipidemia, cardiovascular disease, renal disease, and obesity suggest that either gout, or its necessary precursor hyperuricemia, may play an important role in the manifestations of the metabolic syndrome. In this review, we analyze the complex interconnections between gout and metabolic syndrome, by reviewing gout's physiologic and epidemiologic relationships with its major co-morbidities.
Recent findings Increasing evidence supports gout's association with metabolic syndrome. More specifically, both human studies and animal models suggest that hyperuricemia may play a role in promoting inflammation, hypertension and cardiovascular disease, adipogenesis and lipogenesis, insulin and glucose dysregulation, and liver disease. Fructose ingestion is associated with increased rates of hypertension, weight gain, impaired glucose tolerance, and dyslipidemia and is a key driver of urate biosynthesis. AMP kinase (AMPK) is a central regulator of processes that tend to mitigate against the metabolic syndrome. Within hepatocytes, leukocytes, and other cells, a fructose/urate metabolic loop drives key inhibitors of AMPK, including AMP deaminase and fructokinase, that may tilt the balance toward metabolic syndrome progression. Preliminary evidence suggests that agents that block the intracellular synthesis of urate may restore AMPK activity and help maintain metabolic homeostasis.
Summary Gout is both an inflammatory and a metabolic disease. With further investigation of urate's role, the possibility of proper gout management additionally mitigating metabolic syndrome is an evolving and important question.

Keywords Gout · Metabolic syndrome · Uric acid · Diabetes · Fructose · Hypertension

This article is part of the Topical Collection on *Crystal Arthritis*

✉ Michael H. Pillinger
michael.pillinger@nyumc.org

Gabrielle E. Thottam
thottam.1@buckeyemail.osu.edu

Svetlana Krasnokutsky
svetlana.krasnokutsky@nyumc.org

[1] Department of Medicine, Roger Williams Medical Center, Providence, RI, USA

[2] Crystal Diseases Study Group, Division of Rheumatology, Department of Medicine, New York University School of Medicine, 301 East 17th Street, Suite 1410, New York, NY 10003, USA

[3] Rheumatology Section, Department of Medicine, VA New Harbor Health Care System, New York Campus, New York, NY, USA

Introduction

Despite its ancient provenance, the complexity of gout continues to unravel under ongoing investigation. Gout represents the intersection of multiple intrinsically complex processes: hyperuricemia, urate crystallization, the inflammatory response to this crystallized urate, and the metabolic effects generated by these processes. Beyond acute arthritis, and the tissue deposition of urate, gout is increasingly recognized as a population health problem, based on its increasing incidence and prevalence, impact on healthcare costs, association with co-morbidities, and even impact on mortality.

Over the past several decades, gout's prevalence has risen in parallel with such current epidemics as type 2 diabetes, hypertension, hyperlipidemia, cardiovascular disease, renal disease, and obesity—each of which is also a component or consequence of the metabolic syndrome. Thus, although gout does not comprise a diagnostic criterion for metabolic syndrome, it is at least a "fellow traveler," and potentially an unrecognized element.

Here, we review the complex interconnections between gout and metabolic syndrome. We summarize the known facts about gout's relationship with five major components and/or consequences of metabolic syndrome: hypertension, cardiovascular disease, insulin resistance and diabetes, obesity, and hyperlipidemia/hypertriglyceridemia. Furthermore, we raise the question of whether hyperuricemia and gout arise secondary to the processes of metabolic syndrome, or whether hyperuricemia and/or gout themselves promote a set of cellular processes that predispose afflicted patients to the development of the components of metabolic disease. Finally, we consider the possibility that gout management could ameliorate at least some aspects of metabolic syndrome.

Gout and Metabolic Syndrome: Epidemiologic Clues

Epidemiologic studies indicate that patients with gout experience a higher prevalence of metabolic syndrome than non-gout controls [1]. For example, Yoo et al. examined the prevalence of metabolic syndrome in gout vs non-gout patients applying both the Adult Treatment Panel III (ATP III) and the World Health Organization (WHO) adjusted criteria (Table 1) for diagnosis of metabolic syndrome [1]. Using either set of criteria, gout patients demonstrated a higher frequency of metabolic syndrome than a representative control group. By the WHO adjusted criteria, almost half of the gout population studied were found to have metabolic syndrome.

The prevalences of gout and metabolic syndrome have increased steadily and in parallel with each other. The National Health and Nutrition Examination Surveys (NHANES) of the Centers for Disease Control provide periodic data on diet and illness using stable methodologies that permit comparisons across decades. Using NHANES, Mozumdar and Liguori reported the percent of the population affected by metabolic syndrome in the first decade of the century to be 34.1%, representing an increase of 22.2% from the 27.9% prevalence measured a decade earlier [2]. Similarly, Zhu et al. utilized NHANES to report that the prevalence of gout and hyperuricemia increased by 44.4 and 17.6%, respectively, across a similar time frame [3]. These increases, along with similar increases in several of the individual components of metabolic syndrome, suggest a complex web of relationships that may resist single-target treatment approaches.

To the extent that gout and metabolic syndrome are linked, the question of causality becomes particularly important, since multiple effective and well-tolerated agents are available to control gout, whereas no agents are currently available that target metabolic syndrome as a unitary entity. If proper gout management were to have a salutary impact on metabolic syndrome, it could provide a useful opportunity for intervention.

Hyperuricemia, Gout, and Hypertension

A connection between hyperuricemia, gout, and hypertension was recognized as early as the mid-1800s, when the British physician Dr. Frederick Akbar Mahomed affirmed that "people who are subject to this high blood pressure frequently belong to gouty families or have themselves suffered from the symptoms of the diseases." [4]. Almost two centuries later, we are finally coming to understand that increased levels of serum urate may promote elevated blood pressure, through direct effects on vascular endothelium and by altering the renal system. Population studies extend Dr. Akbar Mahomed's original observation from gout in general to hyperuricemia more specifically. For example, a study reviewing 5564 members of the Thai military reported a strikingly linear relationship between

Table 1 Metabolic syndrome: comparison of ATP III and WHO classification criteria

	ATP III Criteria	WHO Criteria
Criteria	3 or more of 5 criteria	Insulin resistance or diabetes, +2 of 5 additional criteria
Criteria required for diagnosis		Insulin resistance[a]
Obesity	WC ≥102 cm in men, ≥88 cm in women	Waist/hip ratio > 0.90 in men, >0.85 in females; OR BMI >30 kg/m^2
Hyperglycemia	Fasting glucose ≥110 mg/dl	Insulin resistance required for diagnosis
Dyslipidemia	Fasting TG ≥150 mg/dl	TG ≥150 mg/dl OR HDL-C < 35 mg/dl in men, <39 mg/dl in women
Hypertension	BP >130/85 mmHg	BP ≥140/90 mmHg or on pharmacologic treatment
Other	Low HDL-C <40 mg/dl in men and <50 mg/dl in women	Microalbuminuria

WC waist circumference, *BMI* body mass index, *TG* triglycerides

[a] Includes impaired glucose tolerance, impaired fasting glucose, type 2 diabetes

systemic urate concentration and both systolic and diastolic blood pressure [5].

Blood pressure regulation relies on proper functioning of the arterial endothelium and vascular smooth muscle. One critical role for endothelium is the production of nitric oxide, which in vivo diffuses to the smooth muscle layer to promote vasodilation. In in vitro studies, Kang et al. exposed cultured endothelial cells to varying concentrations of urate and measured their ability to produce nitric oxide. They observed that urate, in a dose-dependent manner, had the ability to inhibit endothelial cell nitric oxide production, an effect that was inhibited when urate uptake was blocked by probenecid [6]. In related studies, the same group employed a thymidine incorporation assay to directly test the effect of urate on vascular smooth muscle proliferation. In a dose-dependent manner, urate promoted both smooth muscle proliferation and cell migration [7]. Translated to the in vivo situation, these effects suggest that urate may promote a vascular state in which smooth muscle is hypertrophied and lacks the ability to relax.

One methodology used by cardiologists to assess endothelial function in humans is ultrasound assessment of brachial artery dilation in response to increased blood flow (flow-mediated dilation, FMD) [8]. A blood pressure cuff is placed over the forearm and inflated to 50 mmHg above systolic blood pressure for 5 min. Upon release of the cuff, blood flow is restored, the endothelium senses shear stress and releases nitric oxide, and vasodilation occurs. Subsequently, sublingual administration of nitroglycerine bypasses the endothelium to permit direct measurement of the smooth muscle response (nitrate-mediated dilation, NMD). In studies thus far presented only in abstract form, we have used this technique to analyze untreated gout patients and healthy controls. Our findings indicate a significant impairment of both endothelial and smooth muscle function (FMD, NMD) in untreated gout patients compared to healthy controls ($p = 0.03$). In contrast however, a report by Brook et al. observed no difference in FMD and NMD between gout patients and controls [9], so additional studies will be needed to clarify the impact of gout on vascular function in vivo.

Urate may also affect blood pressure by impacting the kidneys. Elevated levels of urate have been suggested to cause renal tubular injury, interstitial inflammation, and stimulation of the renin-angiotensin system [10]. Studies of evolutionary biology suggest that hominid serum urate levels, which are typically much higher than those of most other mammals, may have evolved in part to promote maintenance of blood pressure in a salt-poor environment [11, 12]. The mechanism of such an event appears to be inactivating mutations in the enzyme uricase, which block the degradation of urate and raise serum urate levels.

To study hyperuricemia and blood pressure in an animal model, Mazzali et al. administered oxonic acid (OA), an inhibitor of rat uricase that promotes elevation in rat serum urate. Subsequent administration of allopurinol, a competitive xanthine oxidase inhibitor that blocks urate synthesis, returned the rats to a normouricemic state [13]. In these experiments, oxonic acid raised, and allopurinol re-normalized rat blood pressure. Similar results have been obtained with febuxostat, which inhibits xanthine oxidase by a non-competitive mechanism [14]. Although these studies suggest a direct effect of urate on blood pressure, alternative explanations (such as direct, urate-independent effects of the drugs under study) cannot be fully excluded.

Can a urate-lowering effect on blood pressure be seen in humans? Potentially yes, at least in carefully selected populations. Such a study was performed by Feig et al., who looked at a population of adolescents with new onset essential hypertension. Otherwise healthy teenagers were enrolled in a placebo-crossover trial and received either allopurinol (400 mgs daily) or placebo for 4 weeks followed by a 2-week wash-out period, followed by a switch to either placebo or allopurinol in the next phase (depending on what was administered in the first phase). After placebo treatment, subjects experienced no change in blood pressure. In contrast, when the subjects received allopurinol, nearly all experienced a decrease in systolic blood pressure, with many achieving normalization. When subjects discontinued allopurinol at wash-out or study end, their blood pressure again increased [15]. Whether similar effects will be observed in hyperuricemic, hypertensive adults remains to be determined, with a trial actively ongoing [16•]. It is possible that individuals with longstanding hypertension develop chronic changes that render their vasculature resistant to urate-lowering responses.

Hyperuricemia, Gout, and Cardiovascular Disease

Despite years of intensive study, cardiovascular disease remains the leading cause of death in the USA [17]. Whether because of direct or indirect effects, numerous studies confirm that patients with hyperuricemia or gout are at increased cardiovascular risk. The Framingham Cohort Study, originally designed to study cardiovascular risk and disease over an extended period, has generated data allowing researchers to analyze the relationship of heart disease to gout. Using the Framingham data set, Abbott et al. observed that men with a diagnosis of gout had increased risk of developing coronary artery disease [18].

If gout confers risk for cardiovascular disease, can treating gout reduce risk? Two large epidemiologic studies by Chen and Pan suggest that patients with gout, or with hyperuricemia without gout, have significantly decreased risk of cardiovascular death when treated with urate-lowering therapy [19••, 20]. Other large data studies have suggested similar findings [21, 22]. There is a pressing need for large prospective clinical

trials to assess whether urate-lowering therapy could be a potential risk modifier in the gout patient population.

Hyperuricemia, Gout, and Insulin Resistance

Patients with gout have an increased prevalence of insulin resistance, which has been well established in the literature [23, 24]. Recent studies raise the question of whether insulin resistance contributes to hyperuricemia and, potentially, gout, or whether the metabolic environment of gout affects insulin resistance and, potentially, diabetes. Intriguingly, epidemiologic studies suggest the latter. Analysis of the Multiple Risk Factor Intervention Trial (MRFIT), a prospective study of 11,351 males with multiple cardiovascular risks, revealed that a current diagnosis of gout is a marker for increased risk for future development of type II diabetes. In contrast, in a study employing the UK Health Improvement Network database, individuals with diabetes were actually at lower risk for future gout than individuals without diabetes [25, 26, 27•]. Since insulin promotes urate retention at the renal tubule [28–30], low levels of insulin in the setting of a diabetic pancreatic failure might contribute to reduced, rather than elevated levels of uric acid.

Is there physiologic evidence that gout or hyperuricemia may promote diabetes? A number of studies, including animal and human models, suggest a connection. In one study, Scott et al. generated hyperuricemic mice by administering a combination of oxonic acid and urate and assessed what changes developed in their serum urate, insulin, and glucose levels. When these mice were hyperuricemic, their insulin levels decreased, and to a lesser but still significant extent, their serum glucose increased. The authors proposed that the findings were due, in part, to urate induction of pancreatic injury [31].

In addition to the pancreas, the liver plays a central role in diabetes, as the primary site of gluconeogenesis. Gluconeogenesis is a complex and highly regulated process, whose rate-limiting enzymes are cytoplasmic phosphoenolpyruvate carboxykinase (PEPCK-C) and glucose 6 phosphatase (G6Pc) [32]. In turn, PEPCK-C and G6Pc are inhibited by the phosphorylated (and hence activated) form of the enzyme adenosine monophosphate kinase (AMPK) [32]. Here, our interest lies in urate's effect on AMPK. Early studies suggest the ability of urate to inhibit AMPK and thus promote gluconeogenesis**.** If correct, these observations raise the possibility that urate-lowering therapy could potentially have an effect on gluconeogenesis, and several studies support the plausibility of this hypothesis.

In rats, exposure to a high-fructose diet induces hyperglycemia, insulin resistance, and elevated serum insulin levels, as well as an increase in serum urate. Intriguingly, treating fructose-fed rats with allopurinol not only lowers urate, but also decreases insulin levels and increases insulin sensitivity [33]. Recently, Takir et al. studied the relationship between urate and insulin resistance in humans and tested the possibility that allopurinol could reduce insulin resistance. In total, 121 subjects were stratified into normouricemic (n = 48) and hyperuricemic (n = 73) groups. The normouricemics were defined as controls, and the hyperuricemic subjects were further subdivided into an observation group (n = 33), and a treatment group receiving allopurinol 300 mg daily. At the end of 3 months, serum urate had declined (as expected) in the hyperuricemic treatment group, but not the untreated hyperuricemic controls. At baseline, insulin resistance was low (measured as HOMA-IR) in the normouricemic control group and higher in both of the hyperuricemic groups. At the end of 3 months, the hyperuricemic control group persisted in insulin resistance, whereas the allopurinol-treated hyperuricemics experienced decreases in insulin resistance, down to a level approximating that of the normouricemic controls [34••].

A Weighty Problem: Hyperuricemia, Gout, and Adipose Tissue

Data from NHANES indicates that that 69.5% of adults ages 20 or older have a BMI consistent with the definition of overweight or obese [17]. The American College of Rheumatology recognizes a relationship between gout and obesity, but that relationship is complex, and confounded by the fact that obesity is generally accompanied by diets that tend to also promote hyperuricemia. That said, data supports the notion that BMI and urate levels may be related by mechanisms that go beyond simply diet.

In an unpublished study of 34 gout patients, we confirmed a significant relationship between urate and BMI (Fig. 1). Somewhat more informative data comes from Kim et al., who compared serum urate levels in type II diabetic subjects, not with BMI (a relatively non-specific measure of overall body fat), but instead, with abdominal visceral and subcutaneous fat deposition using abdominal CT. In so doing, these investigators found no relationship between serum urate and subcutaneous fat—the kind usually thought of when considering obesity. Rather, the investigators found a significant relationship between serum urate and visceral (central) fat—exactly the kind of fat that defines the metabolic syndrome [35].

If fat and urate levels are biologically intertwined, can hyperuricemia be ameliorated through the process of losing fat? The American College of Rheumatology (ACR) Treatment Guidelines recommend weight loss as part of comprehensive gout treatment [36], but diet-based weight loss is notoriously difficult to achieve and sustain, and the impact of such weight loss on serum urate may be difficult to assess due to the long duration of the dieting process and the potential for

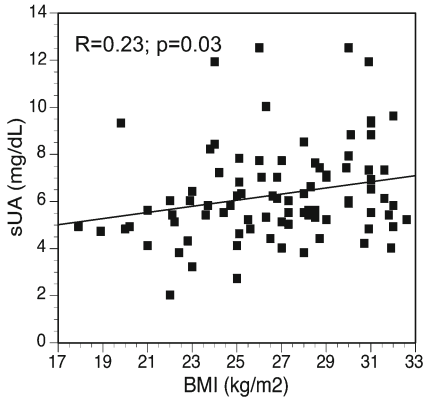

Fig. 1 Relationship between body mass index (BMI) and serum urate (sUA). Eighty-eight patients were assessed for both BMI and sUA, and the relationship plotted. Pillinger et al., unpublished data

confounding events. A more direct impact of weight loss can be inferred from studies examining the impact of bariatric surgery on serum urate. Dalbeth et al. reported that, following bariatric surgery, patients experience a brief and transient period of acute urate increase (possibly related to surgical tissue disruption), followed by a dramatic and persistent urate decrease. In that study, 75% of patients undergoing bariatric surgery achieved a serum urate below 6.5 mg/dL [37•]. Another study by Romero-Talamas et al. reported similar findings, with serum urate levels decreasing significantly post-bariatric surgery. That study also found significant diminishment in the number of gout attacks in the post- versus pre-surgical groups ($P = .005$) [38]. Importantly, bariatric surgery studies may be less likely to be confounded by diet than traditional weight loss studies, since bariatric surgery patients are typically put on very stringent diets both before and after their surgical procedure.

While bariatric surgery studies provide possible evidence of adipose tissue regulating urate levels, the alternative question also deserves consideration: do urate levels play a role in regulating adipose tissue? Baldwin et al. attempted to answer this question using the Pound mouse, a murine model of metabolic syndrome. Pound mice have a genetic mutation in their leptin receptors and develop obesity, insulin resistance, dyslipidemia, liver disease, and hyperuricemia. Baldwin et al. compared these metabolic syndrome mice to otherwise genetically identical wild-type mice. As has previously been reported in humans and other animal models of metabolic syndrome, Pound mice demonstrated a pro-inflammatory phenotype. In particular, compared with the wild-type mice, Pound mice had increased expression of mRNA and protein for macrophage chemotactic protein-1 (MCP-1), a pro-inflammatory cytokine, but decreased expression of adiponectin, an anti-inflammatory cytokine. Intriguingly, treating Pound mice with allopurinol resulted in decreased MCP-1, but increased adiponectin expression, along with the expected decline in serum urate. Thus, treatment with a urate-lowering agent may reverse a pro-inflammatory profile in metabolic syndrome mice [39••].

Compared with the wild-type controls, the abdominal fat of the Pound mice displayed increased macrophage infiltration, a common finding in metabolic syndrome adipose tissue. However, treatment with allopurinol significantly reduced the degree of macrophage infiltration. Consistent with other studies, Pound mice treated with allopurinol also experienced decreased insulin resistance and blood glucose levels and decreased mean arterial pressures. Perhaps disappointingly, Pound mice treated with allopurinol experienced no decrease in overall body weight. However, compared with wild-type mice, the Pound mice showed an increased presence of fatty

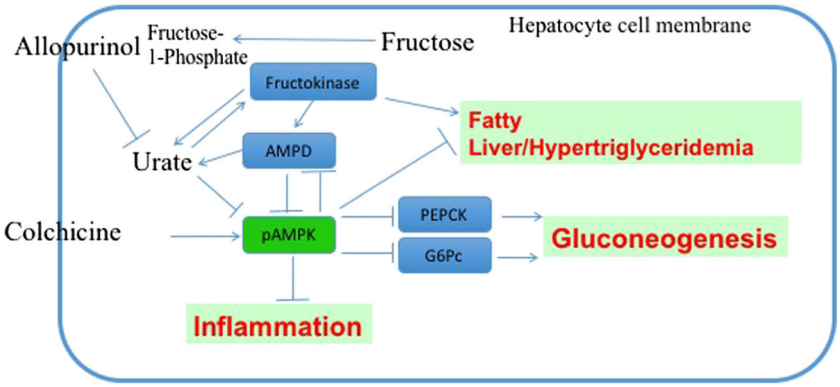

Fig. 2 Theoretical model of the interactions between urate and the mechanisms of metabolic syndrome. Activated, phosphorylated AMP kinase (pAMPK) has inhibitory effects on inflammation, on the rate limiting enzymes of gluconeogenesis, and on the development of fatty liver and hyperlipidemia. Inhibition of pAMPK by AMP deaminase (AMPD) potentially permits metabolic syndrome processes to go forward. AMPD and AMPK are mutually inhibitory, so the balance of their activities may regulate outcomes. Additionally, fructokinase, activated by fructose, promotes fatty liver and activates AMPD, inactivating pAMPK and promoting metabolic syndrome processes. Urate, generated intracellularly as a byproduct of purine catabolism, inhibits pAMPK and again promotes metabolic syndrome processes; urate production is also accelerated by AMPD and fructokinase (feed forward regulation), and urate itself activates fructokinase. Inhibition of intracellular urate generation by allopurinol may therefore promote pAMPK activation and inhibit metabolic syndrome processes. Limited data suggests that colchicine, an anti-inflammatory therapy for gout, may also activate pAMPK. *See text for details*

liver disease (essentially a form of visceral fat deposition), which improved after treatment with allopurinol. These observations correlate well with a human population study reporting that patients with hyperuricemia have almost double the incidence of non-alcoholic fatty liver disease (NAFLD) compared to non-hyperuricemics [40]. Other studies suggest that both the prevalence and severity of NAFLD in hyperuricemic patients are linked to serum urate levels [41]. Whether controlling urate in humans can ameliorate NAFLD remains to be determined.

Putting It Together: the Link Between Fructose, Urate, and Metabolic Syndrome

Fructose consumption has increased dramatically in the past several decades, largely driven by the rise of corn syrup over cane sugar as the preferred commercial sweetener [42]. Fructose ingestion is associated with multiple metabolic syndrome-related impacts, including increased rates of hypertension, weight gain, impaired glucose tolerance, hypertriglyceridemia, and low HDL [43]. In addition, fructose ingestion leads to an increase in intracellular uric acid generation [44]. Biochemically speaking, the impact of fructose on urate is a byproduct of fructose's own metabolism, and the way it interacts with the purine degradation pathways that lead to uric acid generation [45]. During purine catabolism, adenine bases are broken down into hypoxanthine and eventually uric acid; this process is inhibited by the presence of inorganic phosphate (P_i) and adenosine triphosphate (ATP). When a fructose molecule is introduced, it is acted upon by the enzyme fructokinase, during which process ATP is made to donate a Pi (inorganic phosphate), which becomes covalently bound to fructose in the form of fructose 1-P. This process diminishes available levels of both Pi and ATP (indeed, fructose-1-P is sometimes referred to as a phosphate "sink"), and thus, the loss of molecules that can inhibit urate generation. Simultaneously, the degradation of ATP results in the generation of adenosine diphosphate (ADP), which can enter the purine degradation pathway. Thus, the metabolism of fructose results in both the stimulation of urate synthesis, and the loss of regulators of the urate synthetic pathway. In healthy human subjects, this effect can be seen directly with administration of a fructose load, which in a matter of hours can raise the level of serum urate [44]. In retrospective, population-based studies, Choi et al. have demonstrated that drinking sugar sweetened soft drinks (a major source of dietary fructose) correlates with elevated serum urate levels in men and women [46], and with an increased relative risk for gout that was not identified in patients that consumed diet soft drinks [47].

One important metabolic effect of urate is to promote the activation of fructokinase. Thus, in the presence of fructose, urate is generated, which then up-regulates the metabolism of additional molecules of fructose, in a feed forward cycle of fructose metabolism and urate production. In rat studies, Lanaspa et al. demonstrated the ability of urate-activated fructokinase to promote lipid production, again implicating a role for urate in the development of fatty liver. In these studies, feeding rats a high fructose diet led to hyperuricemia, hypertriglyceridemia, hypercholesterolemia, and increased liver weight and fat infiltration—all of which could be partially reversed by treating the rats with the urate-lowering agent allopurinol [48].

One of the critical enzymes for urate production is adenosine monophosphate deaminase (AMPD), whose function is disinhibited in the presence of fructose (since AMPD is inhibited by Pi, whose concentrations decline in the presence of fructose). In addition to promoting urate production, however, AMPD is also an important regulator of AMPK, whose role in inhibiting gluconeogenesis has previously been described. AMPK also plays a role in inhibiting, and AMPD promoting, the development of fatty liver [49]. Wang et al. have additionally shown that AMPK also has anti-inflammatory effects in other cell types, such as leukocytes [50•]. Thus, the complex interactions of urate and fructose metabolism within the cell may well resemble a web, at whose center lies AMPK, whose anti-metabolic syndrome effects are adversely regulated by AMPD, urate, and fructokinase (Fig. 2). The extent to which intracellular inhibitors of urate production (in particular, the xanthine oxidase inhibitors allopurinol and febuxostat) may support the beneficial effects of AMPK remain to be determined, but deserve further study. Intriguingly, Wang et al. have additionally reported that colchicine, the anti-inflammatory agent most commonly used for gout attack prophylaxis, may also act to stimulate AMPK [50•]. The clinical significance of this effect also remains to be determined.

Conclusion

Should the presence of metabolic syndrome and/or its comorbidities lead to more aggressive with gout treatment? Theoretically yes, if urate reduction using xanthine oxidase inhibitors can be proven to ameliorate some or all aspects of metabolic syndrome. The question may be academic however, since the 2012 ACR gout treatment guidelines already recommend that nearly all gout patients, with or without metabolic syndrome, receive a xanthine oxidase inhibitor often along with colchicine [36]. More pressing, perhaps, is the fact that most gout sufferers in fact fail to receive the recommended management [3, 51]. Of approximately 8 million gout sufferers in the USA, only about 5 million have ever received urate-lowering treatment [3, 51, 52], and as few as 0.5 million achieve adequate treatment [53]. Another potentially

important question is whether metabolic syndrome patients with hyperuricemia but no gout also deserve urate-lowering therapy. Treating patients for asymptomatic hyperuricemia is routine practice in some Asian countries. For example, Japanese guidelines recommend the treatment of asymptomatic hyperuricemia, with or without metabolic syndrome, when the patient's serum urate is greater than 9.0 mg/dL [54]. In contrast, the ACR declined to make any recommendation, citing insufficient data. Prospective trials will be critical to clarifying this important question.

In summary, gout is both an inflammatory and a metabolic disease. In properly treating gout in our patients, we may also be treating, and in some cases preventing, their other comorbidities.

Acknowledgements Dr. Pillinger is supported in part by NYU CTSA grant 1UL1TR001445 from the National Center for the Advancement of Translational Science (NCATS), NIH. Dr. Krasnokutsky is supported in part by an Investigator Award from the Rheumatology Research Foundation.

Compliance with Ethical Standards

Conflict of Interest None of the authors have any direct conflict of interest regarding this manuscript. However, for the purpose of full disclosure, we note the following: Dr. Pillinger serves and/or has served as a consultant for Horizon, Ironwood and SOBI, and has been an investigative site for a sponsored, FDA-mandated trial by Takeda. Dr. Krasnokutsky has served as a consultant for Horizon and Ironwood. Dr. Thottam has no disclosures to report.

Human and Animal Rights Informed Consent This review article did not directly involve any clinical research or human subjects. We do reference currently unpublished data from an ongoing study, and note that the study in question has been approved by the Institutional Review Board of New York University School of Medicine.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Yoo HG, Lee SI, Chae HJ, et al. Prevalence of insulin resistance and metabolic syndrome in patients with gouty arthritis. Rheumatol Int. 2011;31(4):485–91.
2. Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. Diabetes Care. 2011;34(1):216–9.
3. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011;63(10):3136–41.
4. Heinig M, Johnson RJ. Role of uric acid in hypertension, renal disease, and metabolic syndrome. Cleve Clin J Med. 2006;73(12):1059–64.
5. Ouppatham S, Bancha S, Choovichian P. The relationship of hyperuricemia and blood pressure in the Thai army population. J Postgrad Med. 2008;54(4):259–62.
6. Kang DH, Park SK, Lee IK, et al. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol. 2005;16(12):3553–62.
7. Kang DH, Han L, Ouyang X, et al. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. Am J Nephrol. 2005;25(5):425–33.
8. Sorensen KE, Celermajer DS, Spiegelhalter DJ, et al. Non-invasive measurement of human endothelium dependent arterial responses: accuracy and reproducibility. Br Heart J. 1995;74(3):247–53.
9. Brook RD, Yalavarthi S, Myles JD, et al. Determinants of vascular function in patients with chronic gout. J Clin Hypertens (Greenwich). 2011;13(3):178–88.
10. Ejaz AA, Mu W, Kang DH, et al. Could uric acid have a role in acute renal failure? Clin J Am Soc Nephrol. 2007;2(1):16–21.
11. Johnson RJ, Gaucher EA, Sautin YY, et al. The planetary biology of ascorbate and uric acid and their relationship with the epidemic of obesity and cardiovascular disease. Med Hypotheses. 2008;71(1):22–31.
12. Álvarez-Lario B, Macarrón-Vicente J. Uric acid and evolution. Rheumatology (Oxford). 2010;49(11):2010–5.
13. Mazzali M, Hughes J, Kim YG, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension. 2001;38(5):1101–6.
14. Pacher P, Nivorozhkin A, Szabó C. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. Pharmacol Rev. 2006;58(1):87–114.
15. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA. 2008;300(8):924–32.
16.• Saddekni MB, Saag KG, Dudenbostel T, et al. The effects of urate lowering therapy on inflammation, endothelial function, and blood pressure (SURPHER) study design and rationale. Contemp Clin Trials. 2016;50:238–44. **This manuscript reports the study design of an improtant trial, currently recruiting patients for participation in an assessment of the potential of urate-lower therapy to control blood pressure in adults with essential hypertension.**
17. United States. Department of Health and Human Services., Center for Disease Control., National Center for Health Statistics (U.S.). Health, United States, 2015 : with special feature on racial and ethnic health disparities, vol. xv. Hyattsville: National Center for Health Statistics; 2016. **449 pages p**
18. Abbott RD, Brand FN, Kannel WB, et al. Gout and coronary heart disease: the Framingham study. J Clin Epidemiol. 1988;41(3):237–42.
19.•• Chen JH, Lan JL, Cheng CF, et al. Effect of urate-lowering therapy on all-cause and cardiovascular mortality in hyperuricemic patients without gout: a case-matched cohort study. PLoS One. 2015;10(12):e0145193. **This study reports the results of an extremely large, "big data"-based study of all-cause and cardiovascular mortality in untreated hyperuricemic patients compared with those receiving urate-lowering therapy on mortality risk. Treated hyperuricemic patients experienced a lower rate of all cause and cardiovascular death, suggesting that uarate lowering therapy may affect survival.**
20. Chen JH, Lan JL, Cheng CF, et al. Effect of urate-lowering therapy on the risk of cardiovascular disease and all-cause mortality in patients with gout: a case-matched cohort study. J Rheumatol. 2015;42(9):1694–701.
21. Grimaldi-Bensouda L, Alpérovitch A, Aubrun E, et al. Impact of allopurinol on risk of myocardial infarction. Ann Rheum Dis. 2015;74(5):836–42.

22. de Abajo FJ, Gil MJ, Rodríguez A, et al. Allopurinol use and risk of non-fatal acute myocardial infarction. Heart. 2015;101(9):679–85.
23. Rathmann W, Funkhouser E, Dyer AR, et al. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: the CARDIA study. Coronary artery risk development in young adults. Ann Epidemiol. 1998;8(4):250–61.
24. Nejatinamini S, Ataie-Jafari A, Qorbani M, et al. Association between serum uric acid level and metabolic syndrome components. J Diabetes Metab Disord. 2015;14:70.
25. Choi HK, De Vera MA, Krishnan E. Gout and the risk of type 2 diabetes among men with a high cardiovascular risk profile. Rheumatology (Oxford). 2008;47(10):1567–70.
26. Rodríguez G, Soriano LC, Choi HK. Impact of diabetes against the future risk of developing gout. Ann Rheum Dis. 2010;69(12): 2090–4.
27.• Kuo CF, Grainge MJ, Mallen C, et al. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Ann Rheum Dis. 2016;75(1):210–7. **This article reports that patients with gout tend to have increasing development of comorbidities after their gout diagnosis, suggesting a possible direction of causality between gout and metabolic syndrome.**
28. Choi HK, Mount DB, Reginato AM, et al. Pathogenesis of gout. Ann Intern Med. 2005;143(7):499–516.
29. Yoo TW, Sung KC, Shin HS, et al. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. Circ J. 2005;69(8):928–33.
30. Quiñones-Galvan A, Ferrannini E. Renal effects of insulin in man. J Nephrol. 1997;10(4):188–91.
31. Scott FW, Trick KD, Stavric B, et al. Uric acid-induced decrease in rat insulin secretion. Proc Soc Exp Biol Med. 1981;166(1):123–8.
32. Rui L. Energy metabolism in the liver. Compr Physiol. 2014;4(1): 177–97.
33. Nakagawa T, Hu H, Zharikov S, et al. A causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol Renal Physiol. 2006;290(3):F625–31.
34.•• Takir M, Kostek O, Ozkok A, et al. Lowering uric acid with allopurinol improves insulin resistance and systemic inflammation in asymptomatic hyperuricemia. J Investig Med. 2015;63(8):924–9. **This small clinical trial tests the possibility that urate lowering in patients with asymptomatic hyperuricemia may directly improve their metabolic state, in the form of decreased insulin resistance, as well as systemic inflammation.**
35. Kim TH, Lee SS, Yoo JH, et al. The relationship between the regional abdominal adipose tissue distribution and the serum uric acid levels in people with type 2 diabetes mellitus. Diabetol Metab Syndr. 2012;4(1):3.
36. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64(10):1431–46.
37.• Dalbeth N, Chen P, White M, et al. Impact of bariatric surgery on serum urate targets in people with morbid obesity and diabetes: a prospective longitudinal study. Ann Rheum Dis. 2014;73(5):797–802. **Dalbeth et al report that weight loss surgery results in clinically relevant reductions in serum urate.**
38. Romero-Talamás H, Daigle CR, Aminian A, et al. The effect of bariatric surgery on gout: a comparative study. Surg Obes Relat Dis. 2014;10(6):1161–5.
39.•• Baldwin W, McRae S, Marek G, et al. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. Diabetes. 2011;60(4): 1258–69. **This study analyzes the effect of urate on a mouse model of metabolic syndrome. The study found that alterations in urate could affect components of the metabolic syndrome, including including insulin resistance and systemic and adipose inflammation.**
40. Shih MH, Lazo M, Liu SH, et al. Association between serum uric acid and nonalcoholic fatty liver disease in the US population. J Formos Med Assoc. 2015;114(4):314–20.
41. Sirota JC, McFann K, Targher G, et al. Elevated serum uric acid levels are associated with non-alcoholic fatty liver disease independently of metabolic syndrome features in the United States: liver ultrasound data from the National Health and Nutrition Examination Survey. Metabolism. 2013;62(3):392–9.
42. Johnson RJ, Segal MS, Sautin Y, et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. Am J Clin Nutr. 2007;86(4):899–906.
43. Perez-Pozo SE, Schold J, Nakagawa T, et al. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. Int J Obes. 2010;34(3):454–61.
44. Johnson RJ, Perez-Pozo SE, Sautin YY, et al. Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? Endocr Rev. 2009;30(1):96–116.
45. Mayes PA. Intermediary metabolism of fructose. Am J Clin Nutr. 1993;58(5 Suppl):754S–65S.
46. Choi JW, Ford ES, Gao X, et al. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. Arthritis Rheum. 2008;59(1):109–16.
47. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ. 2008;336(7639): 309–12.
48. Lanaspa MA, Sanchez-Lozada LG, Cicerchi C, et al. Uric acid stimulates fructokinase and accelerates fructose metabolism in the development of fatty liver. PLoS One. 2012;7(10):e47948.
49. Lanaspa MA, Cicerchi C, Garcia G, et al. Counteracting roles of AMP deaminase and AMP kinase in the development of fatty liver. PLoS One. 2012;7(11):e48801.
50.• Wang Y, Viollet B, Terkeltaub R, et al. AMP-activated protein kinase suppresses urate crystal-induced inflammation and transduces colchicine effects in macrophages. Ann Rheum Dis. 2016;75(1):286–94. **This study underlines the important role of AMPK's on inflammatory response, and suggests a novel mechanism of colchicine as a stimulator of AMPK.**
51. Sarawate CA, Brewer KK, Yang W, et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. Mayo Clin Proc. 2006;81(7):925–34.
52. Riedel AA, Nelson M, Joseph-Ridge N, et al. Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. J Rheumatol. 2004;31(8):1575–81.
53. Edwards NL. Quality of care in patients with gout: why is management suboptimal and what can be done about it? Curr Rheumatol Rep. 2011;13(2):154–9.
54. Yamanaka H. Japanese guideline for the management of hyperuricemia and gout: second edition. Nucleosides Nucleotides Nucleic Acids. 2011;30(12):1018–29.