Review

Urate-Lowering Agents in Asymptomatic Hyperuricemia: Role of Urine Sediment Analysis and Musculoskeletal Ultrasound

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Key Words

Uric acid • Urate nephropathy • Rasburicase • Canagliflozin • Chronic kidney disease

Abstract

Current urate-lowering therapy (ULT) includes three direct acting drugs (allopurinol, febuxostat, Rasburicase) and at least four 'indirect' drugs with other important targets (canagliflozin, losartan, fenofibrate and sevelamer). Moreover, the alcalinization of urines using bicarbonate can be used to dissolve urate crystals and the clinician may discontinue several drugs are known to increase serum levels of uric acid, such as diuretics, aspirin, cyclosporine, theophylline, mycophenolate and ACE inhibitors. While there is a consensus to start ULT in cases of symptomatic hyperuricemia (gout, urate-nephrolithiasis), the very frequent conditions of asymptomatic hyperuricemia remains a major conundrum. The effect of asymptomatic hyperuricemia on kidney function has had fluctuating positions over decades. The conflicting results might indicate: (i) the presence of counterbalancing positive and negative effects on kidney function of both serum uric acid and urate-lowering agents, (ii) the presence of a subpopulation of patients, as yet unidentified, which could truly benefit from a urate-lowering therapy. Therefore, today the treatment of asymptomatic hyperuricemia is not recommended nor excluded by current guidelines. Here we suggest that a possible guide for the treatment of asymptomatic hyperuricemia might be the presence of urate crystals in the urine sediment and/or signs of asymptomatic articular damage by urates, identified by musculo-skeletal ultrasound. Moreover, a watchful analysis of the trend in creatinine/eGFR, proteinuria or urate levels might also guide the clinician. Initiation of ULT and follow-up in cases of asymptomatic hyperuricemia should consider urine sediment analysis, musculoskeletal ultrasound and trends in creatinine, proteinuria and serum urate levels.

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Introduction

The use of urate-lowering drugs is still matter of controversies and of ongoing research. Current knowledge reflects a non-linear path in history with the alternation of different positions. The understanding of this path allows having a clearer picture of the uncertainty of current knowledge.

Discovery of uric acid in the urine and its evolutionary meaning

In 1776 Scheele found a substance characterizing urinary stones, which was afterwards named by Morveau “Lytic acid”. In 1798, Pearson renamed the substance “uric oxide”. Foucroy agreed with Pearson that the term “lytic” was inappropriate and proposed the name “uric acid”, which is still in use today [1]. Uric acid is produced by the enzyme xanthine oxidase (or by xanthine dehydrogenase) from xanthine and hypoxanthine, a reaction important for the scavenging of free radicals [2]. It is degraded by urate oxidase in rodents and pigs, whereas in humans this enzyme is non-functional [3, 4]. Interestingly, humans have lost the uricase gene together with the gene responsible for ascorbate synthesis (a potent antioxidant) [5], whereas rodents cannot loose uricase, as the deletion of urate oxidase gene is incompatible with life (as demonstrated by mouse knock-out experiments) [6]. So why humans can be spared from the need of uricase, whereas other animals need it? Possibly in humans unknown factors contribute to the stability of uric acid in blood and kidneys, thereby preventing a massive damage to the kidneys. Moreover, the increased levels of uric acid in humans might counterbalance the loss of ascorbate. Indeed, uric acid has ‘protective’ properties such as (i) anti-oxidant activity (possibly replacing the loss of ascorbate synthesis) [5, 7], (ii) antinatriuretic and vascular effects mediating blood pressure homeostasis in low-salt environments [4], (iii) neuroprotection, particularly on dopaminergic neurons [8], (iv) modulator of the gut microbiome, whose composition is therefore different in humans from other animals [9, 10] a marker of effective blood volume and antidiuretic hormone levels [11, 12] and an accurate and reliable marker of kidney function [13].

The paradigm of hyperuricemia-gout-nephropathy association

The discovery of the link between uric acid and gout in the early 1900s’ by Garrod [14] led to the concept that uric acid is a toxin responsible for arthritis. Much later, in 1960, uric acid was proposed as a toxin also for the kidney (hence called ‘gouty nephropathy’) [15] and for the cardiovascular system [16, 17]. The hypothesis of uric acid as a nephrotoxic agent gained much success, possibly in wake of still ongoing research on uremic toxins [18].

The main evidences of a link between gout, the disease of rich people due to hyperuricemia, and renal disease at that time are summarized below: (i) histopathology studies: in the late 19th century Garrod showed sodium urate accumulation in the interstitium of the kidney of a patient with gout (post-mortem study) [14]. In 1952 Modern and Meister propose that renal insufficiency, normal blood pressure, without proteinuria, characterized the ‘kidney of gout’ in three patients [19]. In 1960 Talbott and Terplan review 279 autoptic cases of gout revealing renal lesions (pyelonephritic scars, intrarenal tophi, arterial sclerosis, interstitial fibrosis) [15]. Uric acid crystals were thought to form directly in the interstitium; (ii) pathogenetic studies: the kidney of the majority of gouty patients does not eliminate adequately uric acid, which would lead to hyper-uricemia and therefore to gout [20]. The main consequence is that the levels of uric acid would be normal in the tubules of gouty patients but likely increased in the interstitium (where urate deposits were reported). This was consonant

with known properties of tubules in the processing of uric acid and NaCl transport [21]; (iii) experimental studies on animal models: in 1974 experiments on rats treated with oxonic acid, a uricase inhibitor, showed the developed hyperuricemia, hyperuricosuria and renal disease [22].

The data seemed to support the paradigm that, in gout, uric acid would accumulate in the kidney interstitium, forming crystals and leading to kidney fibrosis and renal failure.

A requiem for gouty nephropathy?

Much like the dynamics of scientific discussions described by Kuhn [23], a number of evidences in contrast with the paradigm of a gouty nephropathy started to accumulate. Faced with these evidences, scientists proposed a revision of the paradigm and, later, its rejection. A selection of the evidences against a 'gouty nephropathy' is listed below: (i) uric acid deposits in the kidney occur without gout in 86% of patients [24]; (ii) the animal model with oxonic acid (a) does not develop arthritis (in contrast with gout), (b) shows intratubular (not interstitial) uric acid deposits and (c) presents an acute renal failure (in contrast with the human chronic disease). The results have been replicated using mice genetically lacking uricase, which die after only 4 weeks of age, with a devastating nephropathy from intratubular (not interstitial) urate crystals, very different from the human disease [6].

These findings led to an adaptation of the initial paradigm: hyperuricemia (even without gout) is a cause of kidney injury, thus accounting for the presence of kidney injury in hyperuricemic patients without gout [25]. Again, new evidences started to accumulate, contradicting also the revised paradigm: (i) since 1960 it was known a hereditary form of gout accompanied by a renal nephropathy without uric acid crystals into the kidney [26]; (ii) in 1975 Berger and Yu longitudinally studied gouty patients, showing no modification of kidney function after 11 years of follow up; however kidney function deteriorated in gouty patients with hypertension [27]. In these patients the treatment of hyperuricemia (with allopurinol) did not influence the evolution of the kidney function; (iii) in the 1980s, many patients thought to have chronic urate nephropathy were found to be actually affected by lead nephropathy [28, 29]. These data led Laurence H Beck to write in 1986 an influential paper entitled "Requiem for gouty nephropathy", where a new paradigm was therefore proposed: hyperuricemia, with or without gout, does not induce chronic renal disease and allopurinol treatment does not modify the renal destiny in chronic kidney disease [30]. However, he accepted that an acute, massive hyperuricemia (as in tumor lysis) can cause an "acute uric acid nephropathy"; at variance, gout and renal disease can coexist due to a genetic mutation, without causal relationship between gout and renal disease [31]. The new paradigm offered explanations for previous findings: (i) the old data were based on retrospective cadaveric studies and thus confused cause-effect relationship between gout and nephropathy (kidney disease causes hyperuricemia); (ii) the old retrospective data were affected by a confounding factor: many hyperuricemic subjects were hypertensive, and thus developed nephropathy due to hypertension and not because of hyperuricemia [32, 33]; (iii) moreover mice lacking uricase are not a model of gout, but actually a model of "acute uric acid nephropathy" as in tumor lysis syndrome, due to the large, acute, deposits of uric acid crystals inside tubules, thus leading to acute loss of renal function; (iv) a familial form of "urate nephropathy" (FJHN), caused by a mutation in the uromodulin gene which was responsible for the nephropathy with a consequent hyperuricemia [34]. The term "gouty nephropathy" was, therefore, abandoned and the locution "urate nephropathy" was reserved for the acute disease caused by massive hyperuricemia, such as in tumor lysis syndrome [35].

Urate-lowering therapy (ULT)

During a drug-discovery program aimed at finding new therapies for cancer, in 1956 Robins found the first urate-lowering drug acting as an inhibitor of xanthine oxidase, named allopurinol [36, 37]. Many years later, in 1998, a new urate-lowering drug was discovered, Febuxostat, and licensed in 2008-2009 (brand name: Adenuric) [36]. Interestingly, the Pubmed database reports that, in the years 1980-2000, the number of publications in nephrology increased exponentially, whereas the papers on urate nephropathy decreased following Beck's publication. However, the trend reversed approximately after Febuxostat discovery, with a renewed interest for urate nephropathy. Furthermore, in 2002 a new uric acid lowering drug was introduced, a recombinant urate oxidase named Rasburicase (even though a similar drug, Uricozyme, was already introduced in 1975, but did not encounter much success). Rasburicase found its application in acute urate nephropathy, as in tumor lysis syndrome. In more recent times, canagliflozin, a glycosuric agent inhibiting the glucose transporter SGLT1, was also found to have uricosuric effect [38]. Incidentally, the serendipitous finding that commonly used drugs exert uricosuric effect is not new, such as in the case of losartan [39], fenofibrate [40] and more recently sevelamer [41]. Therefore, three direct acting drugs (allopurinol, febuxostat, Rasburicase) and at least four 'indirect' drugs with other important targets (canagliflozin, losartan, fenofibrate and sevelamer) are today available as urate-lowering therapy (ULT). Moreover, the alcalinization of urines (pH 8) with bicarbonate (50-150 mEq in 1 L of D5W i.v. 1-1.5 L/hour or 325-2000 mg per os, 1-4 times/day) may also be implemented to dissolve urate crystals, which require acidic environment to precipitate [42, 43]. On the flip side, several drugs are known to increase serum levels of uric acid, such as diuretics, aspirin, cyclosporine, and theophylline. Moreover, mycophenolate and ACE inhibitors are reported to induce gout in patients (incidence of 3-10% and <1% respectively) [37, 44].

At present, there is a consensus that in cases of symptomatic hyperuricemia (gout, urate-nephrolithiasis), a ULT should be started, urine alkalinization considered and, when possible, drugs inducing hyperuricemia discontinued. Conversely, the very frequent conditions of asymptomatic hyperuricemia remain a major conundrum for the clinician, principally because, notwithstanding the Beck's Requiem, the relationship between chronic kidney disease (CKD) and hyperuricemia is still a matter of debate. A recent metanalysis conducted by Li et al. [45], based on thirteen studies, concludes that elevated serum uric acid levels represents a risk for the development of chronic renal dysfunction. However, the metanalysis did not include important 'negative' studies, such as the notable "Modification of Diet in Renal Disease" and the "Mild to Moderate Kidney Disease" studies that did not find a link between CKD and hyper-uricemia [46, 47]. Similarly, the metanalyses exploring the link between urate-lowering agents and nephroprotection are quite contrasting [48, 49]. The metanalysis by Bose et al. [48] acknowledges "substantial heterogeneity" among studies, with five trial concluding no effect of allopurinol on GFR and three trials with protective effects, with inconclusive data on the progression to end-stage kidney disease. The presence of such conflicting results raises the suspicion that, if uric acid represents an independent risk factor for CKD, (i) it does not attain to all human subjects but only to a subpopulation and/or (ii) the effect size is small (for example because negative effects of hyperuricemia are partially counterbalanced by positive effects or because urate-lowering agents have adverse effects that counterbalance the reduction of serum uric acid).

Conversely, the excessive decrease of serum uric acid should be avoided due to the increased incidence of neurodegenerative diseases in presence of low uric acid levels [50]. Indeed, uric acid is an important neuroprotective factor for dopamine neurons, thus preventing Parkinson's disease [8]. Historically, it is interesting to remember how the connection between uric acid and the brain started on a false assumption: in the early 1960s'

the observation that men of genius are frequently troubled with gout led to the hypothesis that this was due to the similarity between uric acid and purines, thus stimulating the cerebral cortex [51]. However, the subsequent research found a significant but very low correlation between intelligence (indexed by the IQ) and serum uric acid levels [52–55]. Therefore, current guidelines do not recommend to treat asymptomatic hyperuricemia to slow the progression of chronic kidney disease or CKD (“There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. (Not Graded)”) [56].

Serum Urate and cardiovascular risk

Notably, almost in parallel with the proposal of the gouty nephropathy hypothesis, a completely different paradigm regarding hyperuricemia was being proposed, that is a role of sodium urate in cardiovascular disease. The idea of this association routes back in the late 19th century with Mahomed, Haig, and Davis [57]. After a long hiatus, the uric acid-cardiovascular hypothesis then is presented again around 1950 (again at the same time of the ‘gouty nephropathy’ hypothesis), by the work of Gertler et al. [16]. In 1999 the Framingham study supported the view that uric acid is not a risk factor for cardiovascular disease [58]. This was later confirmed by similarly large studies and metanalysis [59]. Current guidelines (e.g. JNC-8) do not list uric acid as a risk factor. The main reason for this change in direction has been the strong association of uric acid levels and other known risk factors for cardiovascular disease (obesity, diabetes etc.). Interventional studies and metanalysis about urate-lowering therapy on cardiovascular disease do not support this approach to reduce cardiovascular risk [60]. A previous Cochrane review reached the same result, even though it is possible that urate-lowering approach might have an effect on hypertension [61]. Overall, the association between uric acid and cardiovascular disease appear to have the same dynamic of gouty nephropathy. As proposed at the end of the discussion, it is possible that the alternating positions towards this paradigm underline a difficulty to identify a subpopulation that would truly benefit from urate-lowering therapy.

Hints to start a urate-lowering therapy (ULT)

The possibility to identify a subpopulation of subjects particularly prone to urate damage would allow to use urate-lowering agents only on subjects that would really benefit from them. Here we propose to identify subjects at high risk of CKD progression from urates by analyzing (i) the urinary sediment (ii) musculoskeletal ultrasound (iii) longitudinal study of CKD progression rate (Fig. 1). Specifically, urinary sediment should be interrogated for the presence of urate crystals, which would demonstrate supra-saturating levels of uric acid in the kidney. Similarly, the musculo-skeletal ultrasound can identify signs of urate deposition on joints far before any sign of gout is evident at clinical level [62].

Case reports and case series support this claim. Randall reported the presence of uric acid crystals in the urine sediment of a patient with ileostomy with progressive kidney damage, who responded to an oral sodium bicarbonate therapy [42]. A familial form of hyperuricosuria and hematuria, which responded to a therapy with allopurinol, diuretics and fluid intake, was also identified by uric acid crystals in the urine sediment [63]. Moreover, the presence of urate crystals in urine sediment has been identified in the case of Mesoamerican nephropathy [64].

On the other side, asymptomatic urate deposition in joints can be recognized using ultrasound (MSK-US), such as hyperechoic enhancement of the cartilage surface, the double contour image of the cartilage, intra-articular hyperechoic clouds, bone erosion, synovitis,

periarticular power signal [62, 65]. These signs precede articular symptoms (so called 'hidden gout'). The sensitivity/specificity of US in identifying gout in symptomatic patients is quite high: 83%/82% according to Löffler et al. [66], 87.2%/84% according to Bhadu et al. [67], 84%/81% in early gout [68] respectively. In pre-gout (hidden gout), asymptomatic patients, no sensitivity/specificity exists formally because, in this population, there is no

gold standard to compare with. However, we know that 13% of asymptomatic, hyperuricemic patients have identifiable ultrasound modifications on the first metatarsophalangeal joint, whereas only 7% of the normal population shows US abnormalities [69].

In the absence of clear directions for treatment of asymptomatic hyperuricemia, it is reasonable to start ULT in patients with urate precipitates in urines (recognized in the sediment) and in joints (recognized by ultrasound). Therefore, we recommend that research for urate crystals in urine sediment and musculo-skeletal ultrasound (MSK-US) are carried out, as an indication to start ULT and as a follow-up to verify that adequate levels of serum uric acid have been reached.

Finally, another reasonable approach in hyperuricemic patients without signs of urate crystals in urine or MSK-US is a watchful observation of the CKD progression rate (using eGFR, proteinuria or the same levels of serum uric acid) over a period of at least 6-months. Given the absence of data concerning the rate of GFR alterations in hyperuricemic patients, we suggest that in this population controls of serum creatinine should be performed every six months. The measurement of the kidney residual function might also be taken into consideration [70]. If the kidney function is stable and no signs of urates precipitation in urine and joints can be evidences, the clinician might consider to postpone ULT. Vice-versa, in presence of deteriorating kidney function, a challenge with ULT/urine alkalinization may be used and the efficacy evaluated for a minimum of 6 months. If no effect on CKD progression rate is observed, ULT is unlikely to be beneficial for the patient (Fig. 1).

The use of urate-lowering agent should be reserved to high-risk subpopulation, because their use potentially depletes the patient from a neuroprotective factor and reduces the possibility to use uric acid as a marker of kidney function. One possibility to identify a subpopulation of subjects particularly prone to urate damage might be the finding of urate crystals in urine sediment and ultrasound alterations in a musculo-skeletal ultrasound; a challenge with ULT and urine alkalinization is warranted in cases with signs of CKD progression, using as a feedback for the efficacy of the intervention a change in CKD progression rate.

Fig. 1. Proposed algorithm to initiate urate-lowering therapy (ULT).

Conclusion

Treatment of asymptomatic hyperuricemia is not recommended by current guidelines. However, by using urine sediment analysis and musculo-skeletal ultrasound it might be possible to identify a subpopulation of patients which might benefit from urine-lowering agents. Both methods might be also used in the follow-up to verify the therapeutic results.

Disclosure Statement

The authors declare they have no conflicts of interest regarding the publication of this article.

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Viggiano et al.: Urine Sediment and Musculoskeletal Ultrasound in Asymptomatic Hyperuricemia

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