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Review

How should we manage asymptomatic hyperuricemia?

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ABSTRACT

The definition of asymptomatic hyperuricemia remains unclear, as no consensus exists about the serum urate cutoff or the relevance of ultrasound findings. Comorbidities associated with hyperuricemia have increased in frequency over the past two decades. Hyperuricemia (and/or gout) may be a cause or a consequence of a comorbidity. Whereas epidemiological studies suggest that hyperuricemia may be linked to cardiovascular, metabolic, and renal comorbidities, Mendelian randomization studies have not provided proof that these links are causal. Discrepancies between findings from observational studies and clinical trials preclude the development of recommendations about the potential benefits of urate-lowering therapy (ULT) in individual patients with asymptomatic hyperuricemia. The risk/benefit ratio of ULT is unclear. The risk of developing gout, estimated at 50%, must be weighed against the risk of cutaneous and cardiovascular side effects of xanthine oxidase inhibitors. The need for optimal comorbidity management, in contrast, is universally accepted. Medications for comorbidities that elevate urate levels should be discontinued and replaced with medications that have the opposite effect. Therapeutic lifestyle changes, weight loss as appropriate, and sufficient physical activity are useful for improving general health. Whether ULT has beneficial effects on comorbidities will be known only when well-powered interventional trials with relevant primary endpoints are available.

1. Introduction

While the incidence of gout has more than doubled over the past two decades [1], the prevalence of hyperuricemia, which is the main risk factor for gout, has risen only slightly, from 19.1% in 1988–1994 to 21.5% in 2007–2008 in the National Health and Nutrition Examination Survey (NHANES) [2]. This discrepancy proves that hyperuricemia is not the only factor responsible for the mounting incidence and prevalence of gout. The increasing prevalence of hyperuricemia may be ascribable to the expanding obesity epidemic; dietary changes including greater consumption of purine-rich processed foods, alcohol, and fructose; and the increasing use of diuretics. The last 20 years have witnessed substantial rises in the frequencies of comorbidities associated with hyperuricemia (and gout), including hypertension (+15%), diabetes (+19%), renal failure (+17%), hyperlipidemia (+40%), and morbid obesity (+19%) [1]. Hyperuricemia (and/or gout) may be a cause or a consequence of a comorbid condition. The management of comorbidities associated with hyperuricemia therefore deserves careful attention [3,4], particularly when the hyperuricemia is asymptomatic [5], and although proof of a causal link is lacking. Indeed, whereas epidemiological data indicate a link between hyperuricemia and comorbidities, Mendelian randomization studies, which compared the phenotypes of patients with and without genetic susceptibility factors for hyperuricemia, did not produce convincing evidence that hyperuricemia causes cardiovascular, metabolic, or renal disease [6–9]. Nevertheless, in a study confined to patients free of comorbidities in order to eliminate confounding [10], asymptomatic hyperuricemia was associated with a crude hazard ratio of 1.82 for incident coronary events [11].

Another factor that confers importance to asymptomatic hyperuricemia and the associated comorbidities is the independent U-shaped association linking hyperuricemia to mortality. This association persists in both men and women after adjustment for confounders including renal function [12]. These data warrant an appraisal of the best management of patients with asymptomatic hyperuricemia. More specifically, whether and to what extent urate levels should be lowered deserves discussion.

2. From asymptomatic hyperuricemia to gout: selecting the cutoff

Hyperuricemia can be defined based on statistical or physicochemical criteria. A statistical definition, however, is inappropriate, since it would require certainty regarding the pathogenic cutoff,

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i.e., the saturation point, which is the plasma level above which monosodium urate (MSU) can no longer dissolve and therefore crystallizes, in both men and women. The plasma MSU saturation point is usually defined as 6.8 mg/dL (408 μmol/L) or 7.0 mg/dL (420 μmol/L). However, values are lower at temperatures found in the body, i.e., 6.4 to 6.6 mg/dL (384–392 μmol/L) at 37 °C and 6.0 mg/dL (360 μmol/L) at 35 °C (the estimated temperature at the great toe). The MSU saturation point within joint tissues is unknown [13]. The 6.0 mg/dL (360 μmol/L) cutoff is used in the latest recommendations issued by the European League Against Rheumatism (EULAR) [14].

Epidemiological studies may provide information of use for selecting the best urate level cutoff. The incidence rate of a first gout attack increased sharply with urate levels in the Normative Aging Study (NAS) of 2046 initially gout-free males, who were followed for 15 years [15]. The cumulative 5-year incidence rate was 30.5% for baseline urate levels above 10.0 mg/dL (600 μmol/L), compared to 0.6% for the 6.0–6.9 mg/dL (360 to 414 μmol/L) range and 0.5% for values lower than 6.0 mg/dL (360 μmol/L). Nonetheless, among males whose baseline urate level was above 9.0 mg/dL (540 μmol/L), 78% did not develop gout over the next 5 years. In a study of 18,889 participants from four cohorts [16], the cumulative incidence rate increased from 0.6% (95% CI, 0.40%–0.80%) after 3 years to 3.2% (95% CI, 2.8%–3.6%) after 15 years. The 15-year incidence rate increased with baseline urate levels from 1.1% (95% CI, 0.9%–1.3%) for levels < 6.0 mg/dL (360 μmol/L) to 49% (95% CI, 31%–67%) for levels > 10.0 mg/dL (600 μmol/L). Thus, about half the participants whose baseline urate level was above > 10.0 mg/dL did not develop gout. A systematic review of prospective cohort studies showed that the frequency of gout increased from less than 1/1000 person-years for urate levels < 6.0 mg/dL (360 μmol/L) to 70/1000 person-years for urate levels > 10.0 mg/dL (600 μmol/L) [17]. These data establish a role for factors other than the urate level [16] in the development of gout, such as substances that inhibit or facilitate crystal formation when tissue MSU levels are high and/or genetic and environmental factors (e.g., fructose intake) that modulate the inflammatory response to MSU deposits. The available data suggest that sustained urate levels above 6.0 mg/dL (360 μmol/L) increase the risk of gout to an extent that varies with the urate level and the duration of chronic hyperuricemia. The interval from asymptomatic hyperuricemia to tophaceous gout varies from 3 to 42 years (mean, 11 years) [18], and the rate of MSU crystal growth is slow.

Defining the upper limit of the normal plasma urate range as 6.0 mg/dL (360 μmol/L) has the advantage of providing both a cutoff for the risk of gout and a target for urate-lowering therapy (ULT), thereby benefiting the partnership with the patient [13]. However, the urate level cutoff above which the risk of cardiovascular, metabolic, and renal diseases increases has not been determined. In a cohort of young adults, an increased risk of developing hypertension occurred at urate levels below those associated with MSU deposition, i.e. at 57 mg/dL (342 μmol/L) in males and 4.5 mg/L (270 μmol/L) in females [19].

3. Do imaging study findings challenge the definition of asymptomatic hyperuricemia?

Asymptomatic gout (also known as pre-gout or hidden gout) has been defined as imaging study evidence in patients with chronic hyperuricemia of clinically silent MSU deposits [20]. However, neither the risk of nor the time to symptomatic gout development in patients with pre-gout is known [21]. Hyperuricemia is necessary but not sufficient for the development of gout (symptomatic hyperuricemia) [2]. Several ultrasonography or dual-energy computed tomography (CT) studies identified MSU deposits in joints and tendons of 30% to 50% of patients with chronic asymptomatic hyperuricemia (Table 1) [22–32, 33]. Similar proportions of patients with ultrasound MSU deposits were found in a study of patients with early gout [34]. By dual-energy CT, MSU deposits were visible in 20% of patients treated for rheumatoid arthritis (including 70% with seronegative disease), suggesting either the concomitant presence of both diseases or a rheumatoid-like presentation of gout [35]. Finally, whether visible to the naked eye or detected only by imaging studies, focal or diffuse MSU deposits may be painless and completely asymptomatic, particularly when located subcutaneously. Among adult sons of patients with gout, nearly 30% had asymptomatic MSU deposits visible by ultrasonography of the metatarsophalangeal joints [36]. All participants with deposits had urate levels > 5.0 mg/dL (300 μmol/L). Thus, patients with a family history of gout should undergo ultrasonography of the first metatarsophalangeal joints and serum urate assays [36]. MSU deposits are visible as a double-contour sign or as tophi with or without erosions [20,37]. In addition, low-grade inflammation by power Doppler has been demonstrated in one quarter of patients, indicating that MSU crystals can trigger inflammatory pathways (IL-6 et IL-8) in patients with asymptomatic hyperuricemia [29].

These data have prompted the development of a new classification system for the stages of gout [33,38], with the addition of asymptomatic MSU deposits between asymptomatic hyperuricemia without deposits and intermittent gout attacks with deposits. This new ultrasound-based classification may require a reappraisal of ULT indications. The European Medicines Agency (EMA) has approved the xanthine oxidase inhibitor febuxostat for chronic hyperuricemia with MSU deposition. Whether not only gout, but also asymptomatic MSU deposits should be considered when selecting the approved indications of new ULTs deserves evaluation.

4. Do the associations with cardiovascular, metabolic, and renal comorbidities support the treatment of asymptomatic hyperuricemia?

Associations linking hyperuricemia to cardiovascular and renal disease were first reported in the 19th century. Epidemiological and experimental data obtained over the past decade point to strong associations between hyperuricemia and hypertension, cardiovascular events, renal failure, sleep apnea and metabolic disease [5,39–41]. Cell culture and animal studies [42] have provided further evidence that hyperuricemia may be involved in renal failure, hypertension, and metabolic syndrome [8]. However, the long time interval from the onset of hyperuricemia to the onset of cardiovascular and renal comorbidities makes it unclear whether hyperuricemia is a risk marker [43–46] or an independent causal factor [47–50] for non-gout diseases (comorbidities). In addition, although hyperuricemia antedates the comorbidities, reverse causality cannot be ruled out [5]. Box 1 lists the reasons that may explain the discrepancies in the results of epidemiological studies vs. randomized clinical trials regarding the links between hyperuricemia and comorbidities.

4.1. Urate levels and the kidney

Evidence supporting a causal link between urate and renal disease include the induction of hyperuricemia by oxonic acid in rats and the fact that hyperuricemia and decreased renal urate excretion antedate the development of renal disease in patients with familial juvenile hyperuricemic nephropathy [5,51]. Serum urate levels increase with the progression of chronic renal failure, although the causal role for hyperuricemia in this phenomenon is controversial [52,53]. In 16 of 20 epidemiological studies, urate levels were associated with the development or progression of chronic renal failure

Table 1
Findings upon ultrasonography and dual-energy computed tomography in patients with asymptomatic hyperuricemia compared to patients with normal uric acid levels and to patients with gout (modified from [38]).

Authors	Mean UAL in pts with AHU (mg/dL)	US DECT	Findings	Joints imaged	Frequency in the AHU group (%)	Frequency in the normal uricemia group	Frequency in the group with gout
Puig [22]	8.5	US	Tophus	Knees, ankles	12/35 (34)	–	–
Howard [23]	8.0	US	DC/tophus	1st MTPJ	5/17 (29)	1/19 (5)	7/14 (50)
Pineda [24]	8.1	US	DC/tophus	Knees, 1st MTPJ foot	17/100 (17) 25/100 (25) 18/50 (36)	0/104 (0) 0/104 (0) 0/52 (0)	–
DeMiguel [25]	8.5	US	DC or hypo-echoic focus	Knee, foot	11/26 (42)	–	–
Keen [28]	7.0	US	Aggregates DC Tophus PD	Wrist, knee, 3rd MCP, ankle, 1st and 2nd MTPJs	(53.3) (23.3) (15) (36.7)	–	(68.3) (34.1) (26.8) (35)
Reuss-Borst [26]	8.1	US	DC	Wrist, knee Elbow, ankle 1st MTPJ, 1st MCPJ	29/372 (8)	2/192 (1)	44/324 (14)
Stewart [27]	7.7	US	DC Tophus Erosion Effusion Synovitis	1st MTPJ	(36) (0) (2) (22) -	(13) (0) (3) (18) (0)	(37) (13) (33) (9) (2)
Estevez-Garcia [29]	7.8	US	Aggregates DC Tophus Erosions Synovitis	1st MTPJ	2/30 (7) 8/30 (27) 0/30 (0) 2/30 (7) 20/30 (67)	0/31 (0) 0/31 (0) 0/31 (0) 0/31 (0) 14/31 (45)	10/30 (33) 8/30 (27) 15/30 (50) 13/30 (43) 23/30 (77)
Sun [30]	8.1	DECT	MSU deposits	Foot	19/22 (86)	–	79/80 (99)
Dalbeth [31]	9.8	DECT	MSU deposits	Foot	6/25 (24)	–	27/33 (82)
Wang [32]	7.8	DECT	MSU deposits	Foot, ankle	7/46 (15)	–	–

UAL, mean uric acid level; pts, patients; AHU, asymptomatic hyperuricemia; US, ultrasonography; DECT, dual-energy computed tomography; MTPJ, metatarsophalangeal joint; MCPJ, metacarpophalangeal joint; DC, double contour; PD, power Doppler; MSU, monosodium urate.

Box 1: Reasons for discrepancies among studies of associations linking hyperuricemia to comorbidities (modified from [50]).

Hyperuricemia was variably defined (notably between males and females).

Confounders (e.g., fructose intake) were not consistently adjusted for.

Hyperuricemia may be a cause or a consequence of comorbidities.

Observational studies cannot provide proof of causality.

The number of events for the study parameter is low in low-risk populations.

The populations in metaanalyses are heterogeneous.

Sample sizes were small and statistical power limited in randomized clinical trials of urate-lowering therapies.

Urate-lowering therapies may act via several mechanisms including urate lowering and xanthine oxidase inhibition (comparison with a uricosuric is useful).

In Mendelian randomization studies, the populations were heterogeneous and environmental factors were not considered; furthermore, no data exist on the potential effects of genetic polymorphisms on urate-related biological mechanisms.

[54]. In two metaanalyses of 13 and 15 observational studies in 190,718 and 99,205 patients, respectively, hyperuricemia was an independent risk factor for chronic renal failure in patients with normal baseline renal function [55,56]. Hypertension may act as a mediator between hyperuricemia and chronic renal failure [57] and may also be a marker for renal failure [58]. Nonetheless, at least four observational studies found no significant association between hyperuricemia and progression of chronic renal failure [54]. In contrast, in two recent metaanalyses, hyperuricemia was significantly associated with both the risk of acute renal failure and mortality in patients who had chronic renal failure [59,60]

Recent heterogeneous interventional trials [54,61] and two metaanalyses [62,63] suggest promising outcomes with ULT, including slower rates of chronic renal failure progression and glomerular filtration rate decline, a glomerular filtration rate increase from 79 to 92 mL/min, decreased blood pressure, and decreased proteinuria. Nevertheless, the results remain inconclusive [64] with both allopurinol and febuxostat [65]. Vast randomized clinical trials of ULT are needed to determine whether ULT has kidney-protective effects [5]. None of the available clinical trials provides sufficient evidence to recommend ULT in patients with asymptomatic hyperuricemia. In Japan, 84% to 89% of nephrologists are in favor of ULT in patients with asymptomatic hyperuricemia and chronic renal failure stage 3 to 5, whereas in the US only 4% of rheumatologists initiate ULT in patients with asymptomatic hyperuricemia [66]. This discrepancy in prescribing behavior probably stems from differences in knowledge about gout and in the treatment goal (which is to prevent chronic renal failure progression for nephrologists).

4.2. Urate levels and cardiovascular disease

Many epidemiological studies have identified significant associations linking urate levels to both cardiovascular disease and risk factors for cardiovascular disease (hypertension, dyslipidemia, diabetes, obesity, metabolic syndrome, renal failure). Hyperuricemia is viewed either as a risk marker or as an independent risk factor for the development of cardiovascular disease [5,67]. Hyperuricemia was associated with cardiovascular disease in a vast population of patients with asymptomatic hyperuricemia, after adjustment for

Table 2
Pros and cons of urate-lowering therapy in patients with asymptomatic hyperuricemia.

Pros [20]	Cons [75]
May prevent progression to symptomatic gout	50% of patients with AHU do not go on to develop gout [16]
May prevent structural disease progression (erosions)	US of the 1st MTPJ does not show structural damage in patients with AHU [27]
MSU deposits within tissues induce low-grade inflammation	US of the1st MTPJ shows no evidence of inflammation in patients with AHU [27]
Gout may deserve to be defined as the presence of MSU deposits regardless of the presence of clinical manifestations	Imaging study signs of MSU deposition are not entirely specific [37]
Uric acid is involved in the pathogenesis of cardiovascular, metabolic, and renal diseases (high risk patients)	Mendelian randomization studies have failed to confirm that urate levels are linked to comorbidities [6]
Allopurinol therapy has been associated with decreased mortality	Allopurinol therapy has been associated with increased mortality
	The risk/benefit ratio of ULT is unclear; allopurinol induces cutaneous adverse events and febuxostat cardiovascular adverse events
	No interventional studies are available [5] to confirm that ULT improves comorbidities [21]
	No recommendations are available (except in Japan [81])

MSU: monosodium urate; AHU: asymptomatic hyperuricemia; US: ultrasonography; MTPJ: metatarsophalangeal joint; ULT: urate-lowering therapy.

nearly all the common confounders, as well as in patients with heart failure, atrial fibrillation, or coronary artery disease [40]. Coronary artery calcifications by coronary angiography were more severe in patients with asymptomatic hyperuricemia and ultrasound evidence of articular MSU deposits than in patients with hyperuricemia but no deposits and in patients with normal urate levels [68]. Data from animal models and epidemiological studies support a causal link between hyperuricemia and hypertension [50,69]. In prospective cohort studies, treatment refractoriness of hypertension was greater in patients with hyperuricemia, chronic kidney disease, type 2 diabetes, or metabolic syndrome [5].

The hypothesis of a causal link leading from hyperuricemia to hypertension was tested in a randomized placebo-controlled trial in obese adolescents with prehypertension [70]. ULT using a xanthine oxidase inhibitor or a uricosuric significantly decreased systolic and diastolic blood pressure values, by a mean of 10 and 9 mmHg, respectively. Xanthine oxidase produces reactive oxygen species that inhibit the production of nitric oxide, potentially leading to endothelial damage. In observational studies and randomized controlled trials concerning cardiovascular diseases, results were variable antioxydant or lowering urate effect? with xanthine oxidase inhibitors [71]. The latest metaanalysis, in which the included studies had a low-to-fair level of evidence, suggested that xanthine oxidase inhibitors may diminish the incidence of cardiovascular events in high-risk patients but that the cardioprotective effect was lost when allopurinol was given in dosages above 300 mg/d, most notably in combination with furosemide [72]. Heart failure failed to improve with 600 mg of allopurinol [73]. A study based on a Markov state-transition model suggested that allopurinol therapy for asymptomatic hyperuricemia may be more effective in preventing cardiovascular events in males with urate levels > 7.0 mg/dL (420 μmol/L) and in females with urate levels > 5.0 mg/dL (300 μmol/L) [74]. At present, xanthine oxidase inhibitor therapy is neither recommended nor accepted for cardiovascular event prophylaxis in patients with asymptomatic hyperuricemia [75,76].

4.3. Urate levels and metabolic syndrome

In a metaanalysis [77] and a prospective study from Italy [78], each 1.0 mg/dL increase in the serum urate level was associated with a 30% and 50% increase, respectively, in the risk of metabolic syndrome. Furthermore, in the Italian study, each 1.0 mg/dL increase was also associated with an increased risk of fasting glucose elevation and of type 2 diabetes, and this effect was greatest in patients whose age was above the median value [78]. In another study, each 1.0 mg/dL increase was associated with a 6% to 11% increase in the risk of type 2 diabetes [79]. However, a Mendelian randomization study found no evidence of a causal link between hyperuricemia and type 2 diabetes [6]. Similarly, clinical trials have failed to convincingly establish that lowering the urate levels is effective in preventing chronic kidney disease in patients with diabetes [80].

Box 2: Management of asymptomatic hyperuricemia (modified from [69]).

Identify factors causing or contributing to the hyperuricemia (lifestyle factors such as alcohol consumption, obesity, drugs that raise urate levels).

Investigate the patient for a cause to the hyperuricemia.

Identify all comorbidities (body mass index, abdominal circumference, blood pressure, cardiovascular risk score) and ensure that the treatment of each is optimal.

Perform a physical examination and ultrasonography to look for monosodium urate deposits (skin, joints, kidney).

Monitor serum urate levels and renal function at regular intervals.

Perform the following laboratory tests: blood cell counts, liver function tests, serum glucose, lipid profile, renal function tests, and calcium and phosphate levels.

Estimate the fractional excretion of urate and measure urinary pH.

5. Managing asymptomatic hyperuricemia

Box 2 lists the steps to take before initiating treatment.

5.1. Pharmacological urate-lowering therapy (ULT)

Given the discrepancies between observational studies and clinical trials, it is too early to make recommendations regarding the potential benefits of ULT in individuals with asymptomatic hyperuricemia [69]. Table 2 lists the pros and cons of ULT in asymptomatic hyperuricemia. The risk/benefit ratio of ULT in this indication is unclear [75]. Few data are available on the efficacy of allopurinol and febuxostat for treating conditions other than gout. The level of evidence is insufficient to indicate that lowering the urate levels in asymptomatic patients can prevent gout, cardiometabolic disease, or renal failure [75,76]. The EULAR, British Society of Rheumatology, and American College of Rheumatology do not recommend ULT in patients with asymptomatic hyperuricemia [76]. However, the Japanese Society of Gout and Nucleic Acid Metabolism suggests that ULT be initiated in asymptomatic patients whose urate levels are > 8.0 mg/dL (480 μmol/L) [81].

The risk of developing gout must be weighed against the risk of adverse drug effects. Neither allopurinol nor febuxostat are devoid of adverse effects. A study of severe cutaneous adverse reac-

tions in 602 patients entered into a French registry in 2003–2016 showed that the main culprit was allopurinol given for inappropriate reasons (51.9%; 95% CI, 42.3%–61.5%), chiefly asymptomatic hyperuricemia, due to the increasing use of allopurinol to treat comorbidities associated with hyperuricemia [82]. In new allopurinol users, the annual incidences of allopurinol hypersensitivity reactions [83], admission, and deaths were 0.5%, 0.2%, and 0.04%, respectively, and the risk of adverse events was twice as high in patients given allopurinol because of asymptomatic hyperuricemia [82]. Among patients with severe allopurinol-induced toxic epidermal necrolysis, 60% to 86% were being treated for asymptomatic hyperuricemia. A French pharmacovigilance study conducted over 2007–2010 identified 69 cases of drug reaction with eosinophilia and systemic symptoms (DRESS) due to allopurinol, which was the most common cause and was associated with a very high risk of DRESS (odds ratio, 47.6; 95% CI, 35.8–63.2) [84]. With febuxostat the risk of cutaneous reaction seems moderately increased in patients who have a history of allopurinol-induced adverse cutaneous reaction (no cross-reactivity) [85], and DRESS is less common with febuxostat than with allopurinol [86].

Febuxostat and allopurinol have similar adverse event profiles. This similarity extends to the recently reported adverse cardiovascular events. In the CARES study in 6190 patients who were randomized to febuxostat or allopurinol and followed for a mean of 32 months, the main outcome measure was a composite criterion including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary syndrome requiring bypass graft surgery [87]. The proportion of patients meeting this criterion was 10.8% with febuxostat and 10.4% with allopurinol (relative risk [RR], 1.03). However, higher values were found in the febuxostat arm than in the allopurinol arm for all-cause mortality (RR, 1.22; 95% CI, 1.01–1.47) and cardiovascular mortality (RR, 1.34; 95% CI, 1.03–1.73).

Given these data, every effort should be made to avoid prescribing ULT for inappropriate indications, with the goal of preventing severe adverse cardiovascular and cutaneous events. The risk of such events should be disclosed to the patient. In February 2013, the French National Drug Safety Agency (*Agence Nationale de Sécurité du Médicament*, ANSM) modified the summary of product characteristics for allopurinol in order to state clearly that asymptomatic hyperuricemia does not indicate allopurinol therapy.

In contrast, appropriate medical management of comorbidities must be provided to patients with asymptomatic hyperuricemia [4,5,14]. All physical examinations and investigations needed to assess comorbidities should be performed. When possible, drugs that increase urate levels should be discontinued. Examples of such drugs include beta-blockers, angiotensin conversion enzyme inhibitors, angiotensin II receptor antagonists other than losartan, diuretics, and low-dose aspirin. Instead, drugs that increase renal urate excretion should be given [14], such as fenofibrate [88] or atorvastatin for dyslipidemia, losartan or calcium channel inhibitors for hypertension, biguanides and glitazones for diabetes (sodium-glucose cotransporter 2 inhibitors, known as iSGLT2 or gliflozins, are not yet commercially available in France), clopidogrel instead of aspirin, and spironolactone as the preferred diuretic agent whenever possible [89].

5.2. Non-pharmacological treatments

5.2.1. Therapeutic lifestyle changes

Changes in lifestyle factors, notably the diet, can avoid excessive uric acid production [90]. The severely purine-restricted diet is no longer recommended given its limited effectiveness, palatability, and continuation rate. Furthermore, severe purine restriction leads to an increase in the consumption of refined carbohydrates and saturated fats, which in turn result in insulin resistance and elevations in blood levels of glucose, triglycerides, and LDL cholesterol [91].

Dietary advice should focus on preventing cardiovascular disease and metabolic syndrome (obesity and insulin resistance), with urate lowering as a possible added benefit. Hypertension can be combatted by a diet that is high in fruit, vegetables, nuts, legumes, low-fat dairy products, and whole grains, while being low in salt, soft drinks, red meat, and processed meat. In patients with baseline urate levels above 6.0 and 7.0 mg/dL, this diet produced urate level decreases of 1.0 and 1.3 mg/dL, respectively [92]. This effect was obtained within 30 days and was sustained after 90 days [93].

The required dietary changes are very simple and can be summarized in five points: eliminate beer with or without alcohol, strong alcoholic beverages, and soft drinks that contain fructose (as indicated on the label); limit the consumption of animal protein and of a few purine-rich foods, by alternating between lean meat and fish, in moderate amounts; prefer low-fat dairy products: 250 to 500 mL of milk or the equivalent in other diary products supplies 10% to 20% of the protein requirements (1 g/kg/day); allow coffee, including decaffeinated coffee; and encourage vitamin C supplementation (500 to 2000 mg/d, except in patients with a history of oxalate renal lithiasis), which lowers the urate level and provides cardiovascular benefits [94]. The Mediterranean diet, known to produce antioxidant and anti-inflammatory effects, was associated with a 20% reduction in urate levels in a small study of patients with asymptomatic hyperuricemia [95]. Furthermore, in a Spanish population of elderly patients at high cardiovascular risk, better adherence to the Mediterranean diet was associated with a lower risk of hyperuricemia [96].

In patients with gout, however, no proof exists that dietary changes exert therapeutic effects [97,98]. Therapeutic lifestyle changes have only small effects on urate levels but remain valuable to improve general health, given the high frequency of comorbidities in patients with hyperuricemia or gout, who are at particularly high risk for cardiovascular disease. Smoking cessation should be encouraged. All the components of metabolic syndrome should be treated. Finally, realistic weight loss goals (−5% to −15%) should be set and physical activity encouraged.

5.3. Weight loss

Weight loss (>5 kg) achieved by therapeutic lifestyle changes or bariatric surgery has been reported to decrease urate levels by 10.0 to 8.0 μmol/dL [99]. In a systematic review of longitudinal studies in obese or overweight patients with gout, the decrease ranged from 16.8 to 3.0 μmol/dL [100].

5.4. Physical activity

The many benefits of physical activity include increased well-being, chronic disease prevention, mortality reduction, and a favorable multisystemic effect. In 100 postmenopausal Japanese women, a Nordic walking program produced a synergistic association between decreases in urate and triglyceride levels and diminished insulin resistance. [101]. A vast Taiwanese study assessed 467,976 individuals including 25% with urate levels > 7.0 mg/dL (420 μmol/L), comparing active participants (physical activity for 150 minutes per week or for 30 minutes per day at least 5 days a week) to inactive participants [102]. Mortality was 11% lower in active and 27% higher in inactive patients with hyperuricemia compared to patients without hyperuricemia. Activity was associated with a 3.7 mg/dL (222 μmol/L) reduction in urate levels and with a 4- to 6-year life expectancy gain compared to inactivity. The effect of physical activity was the same in patients with and without comorbidities.

Unfortunately, both physicians and patients show poor adherence to these non-pharmacological measures [99], chiefly due to insufficient knowledge about both gout and the benefits of lifestyle changes to overall health. In addition, many physicians have limited interest in nutritional education. Finally, the frequent feeling among patients that they are being blamed for their eating habits decreases adherence.

6. Conclusions

Prescribing ULT (xanthine oxidase inhibitor or uricosuric) to decrease the serum urate level is not currently a priority in patients with asymptomatic hyperuricemia. In contrast, optimal management of cardiovascular, metabolic, and renal comorbidities associated with hyperuricemia is a matter of urgency. Consequently, close cooperation between the primary-care physician and rheumatologist is crucial, and therapeutic patient education should be provided [99]. Interventional trials with sufficient statistical power and relevant primary endpoints [103] are needed to determine whether ULT benefits in terms of comorbidity alleviation can exceed the risk of long-term cutaneous and cardiovascular adverse events. The many unresolved issues include the urate level cutoff above which ULT is in order, the optimal duration of ULT, and whether xanthine oxidase inhibitors or uricosurics should be preferred. A clinical risk score specifically designed for gout, similar to the cardiovascular risk score, might provide useful therapeutic guidance [75].

Disclosure of interest

GC has received honoraria for occasional interventions from Mayoli-Spindler and Grünenthal.

References

[1] Elfishawi MM, Zleik N, Kvrgic Z, et al. The rising incidence of gout and the increasing burden of comorbidities: A population-based study over 20 years. J Rheumatol 2018;45:574–9.
[2] 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;63:3136–41.
[3] Pascart T, Lioté F. Gout: state of the art after a decade of developments. Rheumatology 2018, http://dx.doi.org/10.1093/rheumatology/key002.
[4] Lioté F, Pascart T. From hyperuricaemia to gout: what are the missing links? Nat Rev Rheumatol 2018;14:448–9.
[5] Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med 2017;15:123.
[6] Kei A, Koutsouka F, Makri A, et al. Uric acid and cardiovascular risk: What genes can say. Int J Clin Pract 2018;72:e13048.
[7] Keenan T, Zhao W, Rasheed A, et al. Causal assessment of serum urate levels in cardiometabolic diseases through a Mendelian randomization study. J Am Coll Cardiol 2016;67:407–16.
[8] Johnson RJ, Bakris GL, Borghi C, et al. Hyperuricemia, acute and chronic kidney disease, hypertension, and cardiovascular disease: report of a scientific workshop organized by the National kidney foundation. Am J Kidney Dis 2018;71:851–65.
[9] Li X, Meng X, Timofeeva M, et al. Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. BMJ 2017;357:j2376.
[10] Culleton BF, Larson MG, Kannel WB, et al. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 1999;131:7–13.
[11] Wu J, Lei G, Wang X, et al. Asymptomatic hyperuricemia and coronary artery disease in elderly patients without comorbidities. Oncotarget 2017;8:80688–99.
[12] Cho SK, Chang Y, Kim I, Ryu S. U-Shaped association between serum uric acid level and risk of mortality: a cohort study. Arthritis Rheumatol 2018;70:1122–32.
[13] Bardin T. Hyperuricemia starts at 360 micromoles (6 mg/dL). Joint Bone Spine 2015;82:141–3.
[14] Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29–42.
[15] Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the normative aging study. Am J Med 1987;82:421–6.
[16] Dalbeth N, Phipps-Green A, Frampton C, et al. Relationship between serum urate concentration and clinically evident incident gout: an individual participant data analysis. Ann Rheum Dis 2018;77:1048–52.
[17] Shiozawa A, Szabo SM, Bolzani A, et al. Serum uric acid and the risk of incident and recurrent gout: A systematic review. J Rheumatol 2017;44:388–96.
[18] Saag KG, Mikuls TR, Abbott J. The epidemiology of gout and calcium pyrophosphate dehydrate deposition disease. In: Wortman RL, et al., editors. Crystal-induced arthropathies. New-York: Taylor & Francis; 2006. p. 7–35.
[19] Gaffo AL, Jacobs Jr DR, Sijtsma F, et al. Serum urate association with hypertension in young adults: analysis from the coronary artery risk development in young adults cohort. Ann Rheum Dis 2013;72:1321–7.
[20] Perez-Ruiz F, Marimon E, Chinchilla SP. Hyperuricaemia with deposition: latest evidence and therapeutic approach. Ther Adv Musculoskelet Dis 2015;7:225–33.
[21] Stamp L, Dalbeth N. Screening for hyperuricaemia and gout: a perspective and research agenda. Nat Rev Rheumatol 2014;10:752–6.
[22] Puig JG, de Miguel E, Castillo MC, et al. Asymptomatic hyperuricemia: impact of ultrasonography. Nucleosides Nucleotides Nucleic Acids 2008;27:592–5.
[23] Howard RG, Pillinger MH, Gyftopoulos S, et al. Reproducibility of musculoskeletal ultrasound for determining monosodium urate deposition: concordance between readers. Arthritis Care Res 2011;63:1456–62.
[24] Pineda C, Amezcua-Guerra LM, Solano C, et al. Joint and tendon subclinical involvement suggestive of gouty arthritis in asymptomatic hyperuricemia: an ultrasound controlled study. Arthritis Res Ther 2011;13:R4.
[25] De Miguel E, Puig JG, Castillo C, et al. Diagnosis of gout in patients with asymptomatic hyperuricaemia: a pilot ultrasound study. Ann Rheum Dis 2012;71:157–8.
[26] Reuss-Borst MA, Pape CA, Tausche AK. Hidden gout – ultrasound findings in patients with musculo-skeletal problems and hyperuricemia. Springerplus 2014;3:592.
[27] Stewart S, Dalbeth N, Vandal AC, et al. Ultrasound features of the first metatarsophalangeal joint in gout and asymptomatic hyperuricemia: comparison with normouricemic individuals. Arthritis Care Res 2017;69:875–83.
[28] Keen HI, Davis WA, Latkovic E, et al. Ultrasonographic assessment of joint pathology in type 2 diabetes and hyperuricemia: the Fremantle diabetes study phase II. J Diabetes Complications 2018;32:400–5.
[29] Estevez-Garcia IO, Gallegos-Nava S, Vera-Pérez E, et al. Levels of cytokines and microRNAs in individuals with asymptomatic hyperuricemia and ultrasonographic findings of gout: a bench-to-bedside approach. Arthritis Care Res 2018, http://dx.doi.org/10.1002/acr.23549.
[30] Sun Y, Ma L, Zhou Y, et al. Features of urate deposition in patients with gouty arthritis of the foot using dual-energy computed tomography. Int J Rheum Dis 2015;18:560–7.
[31] Dalbeth N, House ME, Aati O, et al. Urate crystal deposition in asymptomatic hyperuricaemia and symptomatic gout: a dual energy CT study. Ann Rheum Dis 2015;74:908–11.
[32] Wang P, Smith SE, Garg R, et al. Identification of monosodium urate crystal deposits in patients with asymptomatic hyperuricemia using dual-energy CT. RMD Open 2018;4:e000593.
[33] Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. Curr Opin Rheumatol 2014;26:186–91.
[34] Ottaviani S, Allard A, Bardin T, et al. An exploratory ultrasound study of early gout. Clin Exp Rheumatol 2011;29:816–21.
[35] Petsch C, Araujo EG, Englbrecht M, et al. Prevalence of monosodium urate deposits in a population of rheumatoid arthritis patients with hyperuricemia. Semin Arthritis Rheum 2016;45:663–8.
[36] Abhishek A, Courtney P, Jenkins W, et al. Monosodium urate crystal deposits are common in asymptomatic sons of people with gout – the sons of gout study. Arthritis Rheumatol 2018;70:1847–52.
[37] Chowalloor PV, Keen HI. A systematic review of ultrasonography in gout and asymptomatic hyperuricaemia. Ann Rheum Dis 2013;72:638–45.
[38] Dalbeth N, Stamp L. Hyperuricaemia and gout: time for a new staging system? Ann Rheum Dis 2014;73:1598–600.
[39] Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359:1811–21.
[40] Borghi C, Rosei EA, Bardin T, et al. Serum uric acid and the risk of cardiovascular and renal disease. J Hypertens 2015;33:1729–41.
[41] Sharaf El Din UAA, Salem MM, Abdulazim DO. Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: a review. J Adv Res 2017;8:537–48.
[42] Zhu Y, Peng X, Ling G. An update on the animal models in hyperuricaemia research. Clin Exp Rheumatol 2017;35:860–4.
[43] Gagliardi AC, Miname MH, Santos RD. Uric acid: a marker of increased cardiovascular risk. Atherosclerosis 2009;202:11–7.
[44] Kuwabara M, Hisatome I, Niwa K, et al. Uric acid is a strong risk marker for developing hypertension from prehypertension: a 5-year Japanese cohort study. Hypertension 2018;71:78–86.
[45] Feig DI. Uric acid: a novel mediator and marker of risk in chronic kidney disease? Curr Opin Nephrol Hypertens 2009;18:526–30.
[46] Desai RJ, Franklin JM, Spoendlin-Allen J, et al. An evaluation of longitudinal changes in serum uric acid levels and associated risk of cardio-metabolic events and renal function decline in gout. PLOS One 2018;13:e0193622.
[47] Kuwabara M, Bjornstad P, Hisatome I, et al. Elevated serum uric acid level predicts rapid decline in kidney function. Am J Nephrol 2017;45:330–7.

[48] Zhao G, Huang L, Song M, et al. Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis 2013;231:61–8.
[49] Kim SY, Guevara JP, Kim KM, et al. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res 2010;62:170–80.
[50] Neogi T. Asymptomatic hyperuricemia: cardiovascular and renal implications. In: Terkeltaub R, editor. Gout & other crystal arthropathies. Philadelphia: W.B. Saunders; 2012. p. 226–38.
[51] Sánchez-Lozada LG. The pathophysiology of uric acid on renal diseases. Contrib Nephrol 2018;192:17–24.
[52] Johnson RJ, Nakagawa T, Jalal D, et al. Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transplant 2013;28:2221–8.
[53] Zoccali C, Mallamaci F. Uric acid in chronic kidney disease: the quest for causality continues. Nephrol Dial Transplant 2018;33:193–5.
[54] Kumagai T, Ota T, Tamura Y, et al. Time to target uric acid to retard CKD progression. Clin Exp Nephrol 2017;21:182–92.
[55] Li L, Yang C, Zhao Y, et al. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease? A systematic review and meta-analysis based on observational cohort studies. BMC Nephrol 2014;15:122.
[56] Zhu P, Liu Y, Han L, et al. Serum uric acid is associated with incident chronic kidney disease in middle-aged populations: a meta-analysis of 15 cohort studies. PLOS One 2014;9:e100801.
[57] Sedaghat S, Hoorn EJ, van Rooij FJ, et al. Serum uric acid and chronic kidney disease: the role of hypertension. PLOS One 2013;8:e76827.
[58] Sun M, Vazquez AI, Reynolds RJ, et al. Untangling the complex relationships between incident gout risk, serum urate, and its comorbidities. Arthritis Res Ther 2018;20:90.
[59] Xu X, Hu J, Song N, et al. Hyperuricemia increases the risk of acute kidney injury: a systematic review and meta-analysis. BMC Nephrol 2017;18:27.
[60] Xia X, Luo Q, Li B, et al. Serum uric acid and mortality in chronic kidney disease: A systematic review and meta-analysis. Metabolism 2016;65:1326–41.
[61] Bellomo G, Selvi A. Uric acid: the lower the better? Contrib Nephrol 2018;192:69–76.
[62] Su X, Xu B, Yan B, et al. Effects of uric acid-lowering therapy in patients with chronic kidney disease: a meta-analysis. PLOS One 2017;12:e0187550.
[63] Liu X, Zhai T, Ma R, et al. Effects of uric acid-lowering therapy on the progression of chronic kidney disease: a systematic review and meta-analysis. Ren Fail 2018;40:289–97.
[64] Eleftheriadis T, Golphinopoulos S, Pissas G, et al. Asymptomatic hyperuricemia and chronic kidney disease: narrative review of a treatment controversial. J Adv Res 2017;8:555–60.
[65] Zeng XX, Tang Y, Hu K, et al. Efficacy of febuxostat in hyperuricemic patients with mild-to-moderate chronic kidney disease: a meta-analysis of randomized clinical trials: a PRISMA-compliant article. Medicine 2018;97:e0161.
[66] Nakaya I, Namikoshi T, Tsuruta Y, et al. Management of asymptomatic hyperuricaemia in patients with chronic kidney disease by Japanese nephrologists: a questionnaire survey. Nephrology 2011;16:518–21.
[67] Lopez-Pineda A, Cordero A, Carratala-Munuera C, et al. Hyperuricemia as a prognostic factor after acute coronary syndrome. Atherosclerosis 2018;269:229–35.
[68] Andrés M, Quintanilla MA, Sivera F, et al. Silent monosodium urate crystal deposits are associated with severe coronary calcification in asymptomatic hyperuricemia: an exploratory study. Arthritis Rheumatol 2016;68:1531–9.
[69] Paul BJ, Anoopkumar K, Krishnan V. Asymptomatic hyperuricemia: is it time to intervene? Clin Rheumatol 2017;36:2637–44.
[70] Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. Hypertension 2012;60:1148–56.
[71] Okafor ON, Farrington K, Gorog DA. Allopurinol as a therapeutic option in cardiovascular disease. Pharmacol Ther 2017;172:139–50.
[72] Bredemeier M, Lopes LM, Eisenreich MA, et al. Xanthine oxidase inhibitors for prevention of cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 2018;18:24.
[73] Givertz MM, Anstrom KJ, Redfield MM, et al. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the xanthine oxidase inhibition for hyperuricemic heart failure patients (EXACT-HF) sTUDY. Circulation 2015;131:1763–71.
[74] Akkineni R, Tapp S, Tosteson AN, et al. Treatment of asymptomatic hyperuricemia and prevention of vascular disease: a decision analytic approach. J Rheumatol 2014;41:739–48.
[75] Stamp L, Dalbeth N. Urate-lowering therapy for asymptomatic hyperuricaemia: A need for caution. Semin Arthritis Rheum 2017;46:457–64.
[76] Richette P, Latourte A, Bardin T. Cardiac and renal protective effects of urate-lowering therapy. Rheumatology 2018;57:i47–50.
[77] Yuan H, Yu C, Li X, et al. Serum uric acid levels and risk of metabolic syndrome: A dose-response meta-analysis of prospective studies. J Clin Endocrinol Metab 2015;100:4198–207.
[78] Bombelli M, Quarti-Trevano F, Tadic M, et al. Uric acid and risk of new-onset metabolic syndrome, impaired fasting glucose and diabetes mellitus in a general Italian population: data from the pressioni arteriose monitorate e loro associazioni study. J Hypertens 2018;36:1492–8.
[79] Lv Q, Meng XF, He FF, et al. High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies. PLOS ONE 2013;8:e56864.
[80] Gul A, Zager P. Does altered uric acid metabolism contribute to diabetic kidney disease pathophysiology? Curr Diab Rep 2018;18:18.
[81] Yamanaka H. Japanese society of gout and nucleic acid metabolism. Japanese guideline for the management of hyperuricemia and gout: second edition. Nucleosides Nucleotides Nucleic Acids 2011;30:1018–29.
[82] Chaby G, Valeyrie-Allanore L, Duong TA, et al. Severe cutaneous adverse reactions due to inappropriate medication use. Br J Dermatol 2018;179:329–36.
[83] Stamp LK, Barclay ML. How to prevent allopurinol hypersensitivity reactions? Rheumatology 2018;57:i35–41.
[84] Agier MS, Boivin N, Maruani A, et al. Risk assessment of drug-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a disproportionality analysis using the French pharmacovigilance database. Br J Dermatol 2016;175:1067–9.
[85] Bardin T, Chalès G, Pascart T, et al. Risk of cutaneous adverse events with febuxostat treatment in patients with skin reaction to allopurinol. A retrospective, hospital-based study of 101 patients with consecutive allopurinol and febuxostat treatment. Joint Bone Spine 2016;83:314–7.
[86] Adwan MH. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome and the rheumatologist. Curr Rheumatol Rep 2017;19:3.
[87] White WB, Saag KG, Becker MA, et al. CARES Investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 2018;378:1200–10.
[88] Waldman B, Ansquer JC, Sullivan DR, et al. FIELD investigators. Effect of fenofibrate on uric acid and gout in type 2 diabetes: a post-hoc analysis of the randomised, controlled FIELD study. Lancet Diabetes Endocrinol 2018;6:310–8.
[89] Choi HK, Soriano LC, Zhang Y, et al. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. BMJ 2012;344:d8190.
[90] Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. Curr Opin Rheumatol 2010;22:165–72.
[91] Rasheed H, Hsu A, Dalbeth N, et al. The relationship of apolipoprotein B and very low density lipoprotein triglyceride with hyperuricemia and gout. Arthritis Res Ther 2014;16:495.
[92] Juraschek SP, Gelber AC, Choi HK, et al. Effects of the Dietary Approaches to Stop Hypertension (DASH) diet and sodium intake on serum uric acid. Arthritis Rheum 2016;68:3002–9.
[93] Tang O, Miller 3rd ER, Gelber AC, et al. DASH diet and change in serum uric acid over time. Clin Rheumatol 2017;36:1413–7.
[94] Beyl Jr RN, Hughes L, Morgan S. Update on importance of diet in gout. Am J Med 2016;129:1153–8.
[95] Chatzipavlou M, Magiorkinis G, Koutsogeorgopoulou L, Kassimos D. Mediterranean diet intervention for patients with hyperuricemia: a pilot study. Rheumatol Int 2014;34:759–62.
[96] Guasch-Ferré M, Bulló M, Babio N, et al. Mediterranean diet and risk of hyperuricemia in elderly participants at high cardiovascular risk. J Gerontol A Biol Sci Med Sci 2013;68:1263–70.
[97] Holland R, McGill NW. Comprehensive dietary education in treated gout patients does not further improve serum urate. Intern Med J 2015;45:189–94.
[98] Moi JH, Sriranganathan MK, Falzon L, et al. Lifestyle interventions for the treatment of gout: a summary of 2 Cochrane systematic reviews. J Rheumatol Suppl 2014;92:26–32.
[99] Abhishek A, Doherty M. Education and non-pharmacological approaches for gout. Rheumatology 2018;57:i51–8.
[100] Nielsen SM, Bartels EM, Henriksen M, et al. Weight loss for overweight and obese individuals with gout: a systematic review of longitudinal studies. Ann Rheum Dis 2017;76:1870–82.
[101] Kawamoto R, Katoh T, Ninomiya D, et al. Synergistic association of changes in serum uric acid and triglycerides with changes in insulin resistance after walking exercise in community-dwelling older women. Endocr Res 2016;41:116–23.
[102] Chen JH, Wen CP, Wu SB, et al. Attenuating the mortality risk of high serum uric acid: the role of physical activity underused. Ann Rheum Dis 2015;74:2034–42.
[102] Badve SV, Brown F, Hawley CM, et al. Challenges of conducting a trial of uric-acid-lowering therapy in CKD. Nat Rev Nephrol 2011;7:295–300.