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Review

Management of asymptomatic hyperuricemia: Integrated Diabetes & Endocrine Academy (IDEA) consensus statement

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ABSTRACT

Aim: The definition and management of asymptomatic hyperuricemia has been an area of controversy for many decades. Debate persists regarding the benefit of treating all cases of asymptomatic hyperuricemia and hence, unsurprisingly there are no clear clinical practice guidelines from our country.
Participants: Ten members consisting of eminent physicians, endocrinologists, nephrologist and a rheumatologist were selected by the Integrated Diabetes & Endocrine Academy (IDEA) for a closed meeting with the aim to come to a consensus.
Evidence: A literature search was performed using PubMed and Cochrane library following which published articles in indexed peer review journals were selected.
Consensus process: Each participant voiced their opinion after reviewing the available data and a consensus was reached after three meetings by voting.
Conclusion: Recommendations were made on important areas such as definition, investigation and management of asymptomatic hyperuricemia.

1. Introduction

Asymptomatic hyperuricemia is a common entity faced by physicians in day to day practice. Also, blood testing for serum uric acid (sUA) is cheap and easily available in most laboratories leading to sometimes unnecessary testing for uric acid. Although there are clear recommendations on the treatment of gout with urate lowering therapy (ULT), the management of asymptomatic hyperuricemia remains controversial. August international bodies except the Japanese guidelines have not clearly outlined the treatment of asymptomatic hyperuricemia [1–3]. On the one hand unnecessary investigation and treatment has its demerits, but on the other hand the accumulating new evidence regarding the benefits of treatment of hyperuricemia cannot be ignored. Many physicians may not be aware regarding the indications of serum uric acid testing and the possible adverse effects of ULT may also be under recognised. There are no published guidelines on management of asymptomatic hyperuricemia from India. The aim of this consensus meeting was to create clear recommendations to guide the physicians for better patient management while preventing serious adverse effects of therapy.

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2. Methods

The consensus committee was selected by Integrated Diabetes & Endocrine Academy (IDEA) consisted of ten experienced clinicians and pioneers in their fields consisting of physicians, diabetologists, endocrinologists, nephrologist and a rheumatologist. Literature search was performed using online database from PubMed and Cochrane Library. Published articles from reputed indexed peer reviewed journals with preference for meta-analyses and randomized controlled trials were selected. The selected articles were given to all committee members prior to the meeting with focus on important areas such as definition of asymptomatic hyperuricemia, whom to screen for hyperuricemia, consequences of untreated hyperuricemia, benefits of treatment of asymptomatic hyperuricemia and choice of therapy. A closed room meeting took place with all ten members individually giving their opinion on these predetermined questions of interest. After the initial discussion, two more meetings were held and the final draft consensus statement was created after voting.

2.1. Definition of asymptomatic hyperuricemia

Theoretically, the definition of asymptomatic hyperuricemia is an elevated sUA above the upper limit of normal in the absence of symptoms or signs of crystal deposition. However, there is no unanimously accepted cut off for hyperuricemia. Most published guidelines (Table 1) are from the western part of the world whose cut offs might not be applicable to Indians considering the genetic, ethnic and diet variabilities. The physiochemical definition for hyperuricemia is based on the saturation point of Monosodium Urate (MSU) in vitro at 37 °C which is 6.8 mg/dl at a pH of 7. However, at the peripheral joints the variation of temperature and pH can lead to crystal deposition was a lower sUA level (6.0 mg/dl at 35 °C) [4]. Gender specific definition for hyperuricemia used by several investigators (≥7 mg/dl for males and ≥ 6 mg/dl for female) is based on recommendations of a symposium held in Rome, Italy in 1961 [5–7]. The gender difference may be due to lower levels of serum uric acid seen in females due to the hypouricemic effect of estrogen [8]. The statistical definition of hyperuricemia (>2 standard deviations above mean) also has its drawbacks as it can vary among different ethnicities, gender, age and time [9]. The most common laboratory method used for uric acid estimation is by the uricase method which is more specific and has a low cost than the colorimetric method that overestimates the uric acid by around 1 mg/dl [10]. Factors determining uric acid levels are summarized in Table 2.

2.2. Consequence of untreated hyperuricemia (summarized in Table 3)

2.2.1. Gout

The most common consequence of untreated hyperuricemia is MSU crystal deposition and gout. Contrary to the commonly used staging system based on natural history, Dalbeth *et al* have proposed a new staging system for gout based on the pathophysiology of the disease: Stage A: hyperuricaemia, but without evidence of monosodium urate (MSU) crystal deposition or symptoms of gout, Stage B: MSU crystal deposition by microscopy or advanced imaging, but without signs or symptoms of gout, Stage C: MSU crystal deposition with prior or current symptoms of acute gout flares and Stage D: advanced gout requiring specialist interventions. The risk of developing gout increases with the rise in sUA. According to the Boston Normative Ageing Study, there was a 22% increased risk of developing gout over a five year period when the sUA was ≥9 mg/dl [12]. The risk was substantially lower at sUA levels between 7.0 and 7.9 mg/dl and 8.0–8.9 mg/dl, which was 2% and 4.1% respectively over a 5 year period, and was 0.1% annually for a sUA <7.0 mg/dl [12]. However, only 15–20% of people with asymptomatic hyperuricemia develop gout, and hence sUA levels is not only the sole risk factor for developing gout [13]. The other risk factors include increasing age, male gender, increasing BMI, dietary factors (such as red meat and alcohol intake), genetic factors (SLC2A9 and ABCG2 polymorphism) and drugs (diuretics) [14].

2.2.2. Renal calculi

Untreated hyperuricemia is also a risk factor for renal calculi. In a study of 1386 subjects with asymptomatic hyperuricemia followed up for 10 years showed that 0.3% of patients with asymptomatic hyperuricemia developed renal calculi as compared to 0.1% in normouricemic patients [15]. A study on Korean population found that there was a linear relationship between elevated sUA and the risk of developing nephrolithiasis in males which was 1.06 (95% CI, 1.02–1.11) when sUA was 7.0–7.9 mg/dl, which increased to 1.72 (95% CI, 1.44–2.06) for a sUA ≥10 mg/dl [16]. Both uric acid and calcium oxalate stones can be seen in hyperuricemia, of which the latter could be due to decreased excretion of citrate and elevated excretion of calcium in urine [17]. The main cause of formation of urate stone is due to the acidic urine, hyperuricosuria and low urinary volume [18]. Apart from this, oxidative stress and insulin resistance due to hyperuricemia has a role in the formation of uric acid stones [19]. Tanaka et al. (2017) found a worse renal outcome in the form of lower eGFR in patients with urate stones (eGFR = 59 ± 21 mL/min/1.73m2) compared to calcium oxalate stones (eGFR = 66 ± 20 mL/min/1.73m2) regardless of the presence of elevated sUA (P = 0.034). However, there was no statistically significant difference between the prevalence of stage 3 chronic kidney disease (CKD) between the two [20].

2.2.3. Development and progression to CKD

The role of hyperuricemia in causing CKD is still a matter of debate. Apart from being a marker of renal dysfunction, there is also evidence suggesting its role as an independent risk factor for development and progression of CKD [21,22]. A study by Obermeyr et al. (2008) found that the chance of new onset CKD was almost double with sUA between 7 and 8.9 mg/dl (odds ratio 1.74; 95% confidence interval (CI) 1.45 to 2.09) and this risk tripled for a sUA ≥9 mg/dl (odds ratio 3.12; 95% CI 2.29 to 4.25) [23]. Apart for crystal deposition, the mechanism of progression to CKD is most probably due to hyperuricemia inducing oxidative stress, endothelial dysfunction, activation of renin-angiotensin aldosterone system (RAAS) which leads to both systemic and glomerular hypertension. This causes ischemia and macrophage infiltration finally leading to interstitial injury and tubulointerstitial fibrosis [23]. A Mendelian randomization study by Jordan et al did not find any evidence supporting causation CKD and decline in eGFR with elevated sUA [24]

Table 1
Definition of hyperuricemia as recommended by international bodies.

Guideline	American College of Rheumatology Guidelines (2012) [1]	EULAR (2016) [2]	Japanese Guidelines (2011) [3]	IDEA Consensus (2019)
Cut off level for hyperuricemia	6.8 mg/dl or 7 mg/dl	6.0 mg/dl	>7 mg/dl	6.8 mg/dl

Table 2
Factors determining uric acid levels [11].

1. Race
2. Age
3. Sex
4. Time
5. Lab technique

Table 3
Possible consequences and associations of untreated hyperuricemia.

Gout
Renal Stones – Urate and Calcium Oxalate
Development and progression of Chronic Kidney Disease
Cardiovascular disease – Hypertension, myocardial infarction, progression of Cardiac failure
Acute Urate Nephropathy
Obesity, insulin resistance, Type 2 diabetes mellitus, metabolic syndrome

2.2.4. Association with cardiovascular disease

Extensive research has been done to find the association between hyperuricemia and hypertension, cardiovascular disease and cardiovascular mortality. Hypertension is closely linked with hyperuricemia with a relative risk of 1.13 (95% CI, 1.06–1.20) for every 1 mg/dl increase in sUA. A cross sectional study in 255 adults in Bangladesh found a significant correlation between sUA and systolic blood pressure (SBP) and diastolic blood pressure (DBP)[p = <0.001] with an increasing trend for prehypertension and hypertension in both genders with increasing sUA in quartiles (p= <0.01) [25]. The possible mechanisms include oxidative stress and endothelial dysfunction due to decreased NO synthase and plasma NO, activation of RAAS and increased inflammation [26]. First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study found that the serum uric acid level was predictive of mortality from ischemic heart disease among females, but no associations were seen among males [27]. However, the Framingham Heart Study indicated that uric acid did not have a causal role in the development of CHD [28]. Gender difference have been also reported from other studies which reveals a higher cardiovascular mortality in females compared to males [29]. A study of 80 patients with coronary artery disease (CAD) from Nagpur, India found a significant association between sUA and severity of CAD assessed by coronary angiography [30]. With regards to heart failure, sUA was found to be a strong prognostic marker in patients with chronic moderate to severe heart failure (NYHA class III or IV) with a relative risk of death of 7.4 when sUA was >9.5 mg/dl but its association with incident heart failure remains to be a matter of debate [31].

2.2.5. Acute urate nephropathy

Acute Kidney Injury (AKI) secondary to sudden and marked increase in sUA (Acute Urate Nephropathy) is a well-known entity which usually occurs following chemotherapy for myeloproliferative and lymphoproliferative malignancies (Tumour Lysis syndrome) and in diseases with excessive production and secretion of uric acid (Lesch–Nyhan or Fanconi syndrome) [17].This occurs due to the precipitation of uric acid leading to the obstruction of the renal tubules and urine outflow tract.

2.2.6. Metabolic syndrome

There is growing evidence showing an association between hyperuricemia and metabolic syndrome it could possibly be used as a marker for its prediction [32,33]. Studies by Chen et al. and Cicero et al. have found significant correlation with serum uric acid and components of metabolic syndrome in adults [34,35]. Patients with hyperuricemia had a 1.6 times increased risk of developing metabolic syndrome [34]. The role fructose in the development of

Table 4
Commonly used drugs known to cause hyperuricemia.

Diuretics – Loop and thiazide diuretics [32]
Antitubercular drugs – Pyrazinamide and ethambutol [33,34]
Low dose Aspirin (≤325 mg/day) [35]
Immunosuppressants – Cyclosporine, Tacrolimus [36]
Nicotinic Acid [37]
Cancer Chemotherapeutic Agents – Tumour Lysis Syndrome [38]
Levodopa [39]
Testosterone [40]

Table 5
Non-Pharmacological management of asymptomatic hyperuricemia.

Detrimental	Beneficial	No restriction
Animal Protein – Red meat, Organ meat (Liver), Seafood, shellfish	Coffee and caffeinated drinks	Vegetable protein- peas, lentils, beans, spinach, mushrooms and asparagus
Alcohol intake – Beer and liquor	Cherries	Red wine in moderation
Sweetened soft drinks and juices, fructose, table sugar	Vitamin C	
Sudden weight loss	Gradual weight reduction Moderate	
Vigorous exercise	Exercise	
Dehydration		

hyperuricemia and metabolic syndrome has been studied in the past. Fructose once ingested enters hepatocytes, following which it is rapidly phosphorylated by fructokinase C to fructose 1 phosphate. This leads to intracellular elevation of AMP and fall in GTP, ATP and phosphate. This leads to activation of AMP deaminase and which is finally metabolised into uric acid [36–40]. Nakagawa el al (2006) found that treatment of fructose fed rats with allopurinol and benzbromarone was able to prevent metabolic syndrome [41]. There are also similar studies in humans studying the effect of ULT on metabolic syndrome which has showing contrasting results [42–44]. All these are small pilot studies and further data is needed to prove causation[45].

2.3. Whom to screen for hyperuricemia

The general perception among physicians and patients is that testing for serum uric acid and its treatment with urate lowering agents is cheap and without hazards, which may not be entirely true. This results in unnecessary testing for uric acid when it is not indicated (for example in patients with aches and pain, polyarthritis, inflammatory arthritis etc). Routine screening for hyperuricemia is not recommended as the natural course of patients with asymptomatic hyperuricemia is not well established.

Recommendation 1:

Whom to screen for hyperuricemia.

1. History of acute monoarthritis suggestive of gout
2. History of chronic gout or tophi
3. As a part of work up for urolithiasis
4. Patients with malignancies specially when receiving cancer chemotherapy
5. Patients receiving drugs known to cause hyperuricemia (summarized in Table 4)
6. Chronic Kidney Disease (eGFR < 60 ml/min/1.73 m^2 and below)
7. Cardiovascular Diseases
8. Metabolic Syndrome

2.4. Ideal way to collect samples for serum uric acid?

There are many factors known to influence sUA level, however whether these factors influence a particular sUA report is unclear. Vigorous exercise is known to increase uric acid levels while moderate to light exercise reduces sUA levels [46]. Ethanol intake especially beer is known to elevate serum uric acid [47]. Smoking is known to be associated with a lower serum uric acid which is attributed to the inactivation of xanthine oxidase [48]. Apart from these, diet, drugs (e.g. some antihypertensives), state of hydration of the patient, and method of testing are also known to influence the sUA [49].

Recommendation 2:

Blood sampling should be done after an overnight fast, avoiding ethanol intake, smoking, vigorous exercise and drugs from the previous night.

2.5. Are there any benefits of urate lowering therapy in asymptomatic hyperuricemia

2.5.1. Rheumatological point of view

Whether treatment of patients with asymptomatic hyperuricemia prevents gout is still unclear. The American College of Rheumatology (ACR) 2012 and the European League Against Rheumatism (EULAR) 2016 guidelines have not given clear recommendations for treatment of asymptomatic hyperuricemia [1,2]. With the advent of newer modalities like musculoskeletal ultrasound, urine sediment analysis to look for urate crystals, early MSU deposition may be identified [50,51]. MSU deposits may be seen in close to 25% of patients with hyperuricemia on imaging however, whether these deposition can progress to clinical gout remains to be seen [52,53].

2.5.2. Progression of chronic kidney disease?

Apart from experimental and epidemiological studies [21–23], there is emerging evidence from clinical trials showing that urate lowering therapy in patients with asymptomatic hyperuricemia may possibly retard the progression of CKD. The most recent meta-analysis which included 832 CKD patients (mainly stage 3–4) showed benefit with urate lowering therapy in patients with asymptomatic hyperuricemia by retarding the fall in eGFR in the treatment arm [54]. A retrospective study of 183 patients from Hyderabad, India with CKD (eGFR <90 ml/min/m^2) and hyperuricemia found that patients who received allopurinol had no significant change in eGFR at 6 months (35.6 ± 13.21 ml/min/m^2, p = 0.5), 1 year (35.2 ± 13.25 ml/min/m^2, p = 0.6) and 2 years (35.01 ± 13.4 ml/min/m^2, p = 0.4) compared baseline (35.43 ± 13.84 ml/min/m^2) but controls had significant fall in eGFR [55]. They also found that allopurinol group had a significant decrease in proteinuria at 6 months, 1 year and 2 years compared to baseline however, although proteinuria increased in control group at 2 years compared to allopurinol group, it was not statistically significant [55]. Bose et al. studied 476 participants with CKD treated with allopurinol which showed no significant improvement in eGFR between treatment and control groups [56]. Although allopurinol has been the gold standard treatment for management of hyperuricemia and gout, the dose modifications required in CKD, increased risk serious cutaneous adverse reactions, and the advent of other uric acid lowering drugs, have all together caused a decline in its usage in CKD. Majority of the more recent clinical trials have favoured febuxostat which has been found to be relatively safer in patients with CKD [57,58]. Lee JW et al. studied 141 patients with stage 3 CKD and hyperuricemia out of which 30 received febuxostat, 40 received allopurinol and the remaining received no ULT [57]. The overall baseline was eGFR 42.1 ± 8.8 mL/min/1.73 m^2 and serum uric acid 8.6 ± 1.5 mg/dL. Febuxostat group showed a significantly lower mean sUA compared to the allopurinol and no ULT groups (5.7 ± 1.0 vs. 7.1 ± 1.2 vs.8.0 ± 0.8 mg/dL, p < 0.001) on follow up. The mean eGFR was also higher in the febuxostat group compared to the other groups at 1 year follow up (47.4 ± 12.6 vs 39.6 ± 15.0 vs 34.3 ± 10.8 mL/min/1.73 m^2, p=<0.001) and this was maintained for a follow up period of four years (42.2 ± 15.7 vs. 25.4 ± 18.5 vs 26.6 ± 16.5 mL/min/1.73 m^2, p = 0.037) [57]. In a one year cohort study on patients with stage 4 CKD and hyperuricemia on ULT, patients who were switched from allopurinol to febuxostat has a statistically significant difference in sUA levels (5.7 ± 1.2 vs 6.6 ± 1.1 mg/dl, p=<0.01) and eGFR (25.7 ± 11.3 vs 19.9 ± 9.5 mL/min/1.73 m^2, p=<0.05) at 12 months compared to patients who were continued on allopurinol (58).Sircar et al. in a double blind randomized control trial comparing febuxostat and placebo in patients with asymptomatic hyperuricemia and CKD stage 3 and 4 found that there was no significant fall in eGFR in the febuxostat

group from baseline (eGFR 31.5 ± 13.6 to 34.7 ± 18.1 mL/min/1.73 m^2 at 6 months, p = 0.3) compared to the placebo group (eGFR 32.6 ± 11.6 to 28.2 ± 11.5 mL/min/1.73 m^2 P = 0.003) [59]. The FEATHER trial by Kimura *et al* studied 467 patients with stage 3 CKD and asymptomatic hyperuricemia [60]. They found that there was no significant difference in mean eGFR slope between the febuxostat (0.23 ± 5.26 mL/min/1.73 m2 per year) and placebo (−0.47 ± 4.48 mL/min/1.73 m2 per year) groups (difference, 0.70; 95% CI, −0.21 to 1.62; P = 0.1) [60]. However, a subgroup analysis in patients with CKD without proteinuria revealed a higher eGFR [Group difference, 1.79 (95% CI, 0.55–3.03)mL/min/1.73 m2 per year (P = 0.005)] and lower creatinine[Group difference, 1.76 (95% CI, 0.44–3.07) mL/min/1.73 m2 per year (P = 0.009)] in the febuxostat group compared to placebo [60]. Febuxostat was also well tolerated in post renal transplant recipients and had a quicker reduction in sUA compared to allopurinol (% change in sUA −52.92 ± 14.82% vs −41.79 ± 15.28%, p = 0.002) at day seven of treatment [61]. In a recent meta-analysis which included four randomized controlled trials, febuxostat showed a statistically significant change in level of sUA (p < 0.001) and albuminuria (p = 0.02) compared to allopurinol however, changes in eGFR was significant only at 1 month follow up and not at 3 months [62]. However, the recently published CARES trial comparing the cardiovascular safety of febuxostat and allopurinol therapy in patients with gout and cardiovascular disease showed a statistically significant increase in all cause death (hazard ratio, 1.22 [95% CI, 1.01 to 1.47], p = 0.04) and cardiovascular death (hazard ratio, 1.34 [95%CI, 1.03–1.73], p = 0.03) in patients who received febuxostat [63]. This has to be kept in mind as patients with CKD are also at risk of having cardiovascular disease [63].

Recommendation 3:

Possible benefits of urate lowering therapy as far as progression of CKD is concerned, is seen in patients in stage 3 −4 CKD with asymptomatic hyperuricemia. Febuxostat may be preferred over allopurinol considering the necessity of dose modification and the increased risk of serious cutaneous adverse reaction with allopurinol.

2.5.3. Cardiovascular disease

Some benefits have been seen with the use of ULT in patients with asymptomatic hyperuricemia and hypertension. Adolescents with hyperuricemia and hypertension were found to have a significant reduction in both systolic BP (mean reduction −6.9 mm Hg [95% CI −4.5 to −9.3 mm Hg] p value = 0.009) and diastolic BP mean reduction −5.1 mm Hg [95% CI −2.5 to −7.8 mm Hg] p value = 0.05) when treated with allopurinol vs placebo in a randomized controlled cross-over study [64]. Qu et al. in their meta-analysis found that patients treated with allopurinol had greater reduction in SBP (0.321, 95% confidence interval [CI]: 0.145 to 0.497, P < 0.001) and DBP (0.260, 95% CI: 0.102 to 0.417, P = 0.001) compared to controls. The SBP reduced regardless of receiving antihypertensive therapy and this was seen with a low dose of allopurinol (<300 mg/dl) [65]. Similar results were also seen in older individuals (>65 years) [66]. Following the publication of the CARES trial mentioned above, the use of febuxostat in patients with cardiovascular disease and high cardiovascular risk is controversial although it has BP lowering in a recent phase 2 randomized controlled trial [63,67].

Allopurinol has also shown to decrease oxidative stress and endothelial dysfunction which thereby may help lower the risk of atherosclerosis, incident myocardial infarction, peripheral arterial disease and ischemic stroke [68–72]. However, most of these studies conducted are small and were registry based and hence further prospective randomized trials are required. Xanthine oxidase inhibitors failed to improve ejection fraction and exercise capacity with moderate to severe heart failure [73,74].

Recommendation 4:

Although benefit is seen with regards to hypertension and lowering risk of cardiovascular disease, we recommend against starting ULT in patients with asymptomatic hyperuricemia and cardiovascular disease until further larger randomized controlled trial reports are available.

2.6. Treatment of asymptomatic hyperuricemia?

2.6.1. Non pharmacological treatment (summarized in Table 5)

This mode of management should be initiated when the upper level of normal sUA is breached irrespective of whether the patient is on ULT. This includes mainly dietary restrictions and exercise. Dietary intake of purine rich food is known to be associated with hyperuricemia. This includes namely animal protein (red meat and organ meat) and seafood protein (fish and shellfish). There is no association between purine rich vegetables (peas, lentils, beans, spinach, mushrooms and asparagus) and development of gout. There is also no association of total protein intake and sUA. Intake of low fat milk and milk products were found to be associated with a lower sUA [75,76]. Alcohol intake also need to be restricted. Beer has been found to increase sUA the most followed by liquor. Red wine taken in moderate amount has not been shown to increase sUA [47]. Intake of sweetened soft drinks, fruit juices, corn syrup and table sugar rich in fructose is also associated with hyperuricemia [77]. Coffee possibly has a beneficial role in decreasing sUA but this is not seen with tea intake [78]. Intake of cherries and vitamin C is also found to have a beneficial role in reduction of uric acid [79]. Uric acid has a close association with BMI and metabolic syndrome. Gradual weight loss by dietary restriction and exercise was found to be more beneficial since sudden weight loss can increase sUA by development of ketosis [79]. Weight reduction by moderate aerobic exercise is found to be associated with a lower sUA whereas vigorous severe exercise may temporarily increase the uric acid levels [80]. One should keep themselves adequately hydrated while exercising as dehydration due to profuse sweating can cause hyperuricemia and precipitate gout in susceptible individuals [81].

2.6.2. Pharmacotherapy

Despite the accumulation of benefits of management of asymptomatic hyperuricemia, urate lowering therapy is not without its adverse effects. Allopurinol induced dermatological reactions such as Stevens-Johnson Syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS) and allopurinol induced hypersensitivity are severe and life threatening. The incidence of allopurinol-induced severe cutaneous adverse reaction (SCAR) is around 0.69 (95% CI: 0.52, 0.92) per 1000 person-years [82]. The use of febuxostat has also come under the scanner with the recent CARES trial as detailed above.

Considering the risk benefit ratio, we recommend starting urate lowering therapy once the sUA is ≥ 9 mg/dl which is similar to the

Japanese guidelines [3]. We recommend starting urate lowering therapy for sUA 7.0–8.9 mg/dl only in the presence renal stones or stage 3 CKD or worse (eGFR <60 ml/min/1.73 m^2). We recommend the use of allopurinol as the 1st line agent in patients with normal renal function ($\geq$ 90 ml/min/1.73m^2) and sUA $\geq$ 9 mg/dl. As a higher starting dose is associated with a higher risk of cutaneous drug reactions, we recommend starting on a low dose 50–100 mg/day and slowly titrate based on the achievement of target sUA [2]. If target is not achieved or patient is not able to tolerate allopurinol, the therapy may be switched to febuxostat. In patients with chronic kidney disease, the main aim of therapy is to prevent gout and possibly to prevent progression of CKD. Febuxostat is considered safe in CKD as it is metabolised by the hepatic route and it has renal benefits which are as good or perhaps better than allopurinol and hence we recommend that it should be used as a first line agent in CKD patients [62]. Starting dose for Febuxostat is 40 mg/day once daily, which can be titrated gradually in order to achieve target [83].

Recommendation 5:

Non pharmacological treatment with diet restriction and exercise is recommended for all patients with asymptomatic hyperuricemia.

In patients with asymptomatic hyperuricemia with normal renal function (eGFR $\geq$ 90 ml/min/1.73m^2) we recommend allopurinol as the 1st line of therapy when sUA is $\geq$ 9 mg/dl. It is to be started at a low dose 50–100 mg/day and titrated slowly according to the target sUA. HLA-B*58:01 testing if available can be done prior to starting allopurinol.

In patients with CKD we recommend staring febuxostat as the 1st line of therapy considering the dose modification required and higher risk of serious adverse outcome of allopurinol. It is to be started at a dose of 40 mg/day and titrated slowly according to the target sUA.

Caution to be exercised in patients with CKD while starting febuxostat as CKD is commonly associated with cardiovascular disease.

2.6.3. Others

Avoid drugs known to cause hyperuricemia. One can consider switching antihypertensives from diuretics to angiotensin receptor blockers (ARB) such as losartan or calcium channel blockers (CCB) [84].

Uricosuric agents like probenecid and benzbromarone are second line agents in management of gout but its role in asymptomatic hyperuricemia is still unknown. These drugs have gone out of favour due to newer agents with better efficacy and safety profile [85].

Table 6
Commonly used cardiometabolic drugs known to have urate lowering properties.

Antihypertensives	• Angiotensin receptor blockers-Losartan [79] • Calcium channel blockers [80]
Oral anti-diabetics	• Metformin [81] • SGLT2 inhibitors [82]
Lipid lowering agents	• Statins [81] • Fenofibrate (83)
Anorectic agents	• Orlistat [84] • Sibutramine [84]
Anti-platelets	• High dose aspirin [81,83]

Drugs commonly used in cardiometabolic practice having urate lowering properties are summarized in Table 6.

2.7. What is the target of uric acid and how long to treat?

Based on the guidelines provided by the EULAR 2016, we also recommend the target of therapy with ULT should by < 6 mg/dl [2]. In patients known to have gout, the treatment is lifelong. However, the definite duration of treatment of patients with asymptomatic hyperuricemia is still unknown. A level of uric acid less than 3 mg/dl is not recommended for a long period as lower levels of uric acid is known to be associated with neurodegenerative diseases such as Parkinson's Disease, Alzheimer's disease and Motor neurone disease [2,86–88].

Recommendation 6:

Target for sUA for patients on therapy for asymptomatic hyperuricemia is < 6 mg/dl.

A sUA of less than 3 mg/dl should be avoided over a long period of time.

Fig. 1 depicts the algorithm for the management of asymptomatic hyperuricemia.

3. Conclusion

Although most of the international guidelines are still are not clear regarding treatment of patients with asymptomatic hyperuricemia, the new evidence from various clinical trials have shown possible benefit in certain areas particularly pertaining to nephroprotection in a setting of CKD. Although testing for hyperuricemia and treatment is cheap, we must individualize the therapy for each patient considering the potential serious although uncommon adverse effects of xanthine oxidase inhibitors. More robust randomized controlled trials which are adequately powered, double blinded having focussed primary outcome measures are needed to address the issue of a broad-based blanket pharmacologic therapy of asymptomatic hyperuricemia. In asymptomatic hyperuricemia, prescribing urate lowering agents for the sole purpose of reducing

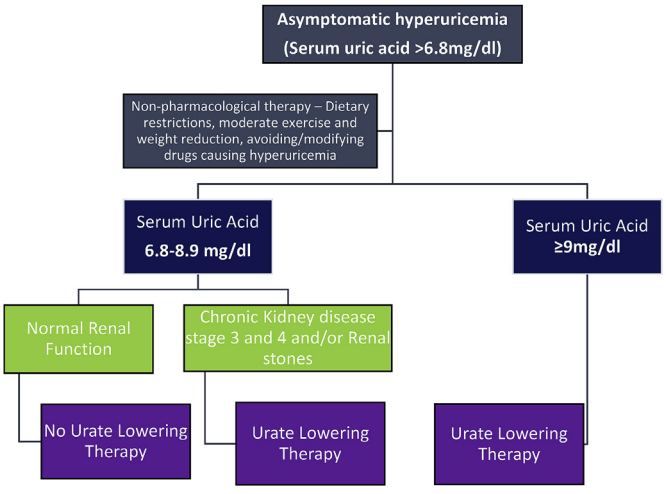

Fig. 1. Algorithm for the management of asymptomatic hyperuricemia.

serum uric acid is not the priority. Whereas, optimal management of cardiovascular, metabolic, and renal comorbidities associated with hyperuricemia is a matter of urgency. Pending availability of further data, the practice of wanton prescription of pharmacologic urate lowering therapy as a panacea for almost all rheumatologic problems in the face of modestly elevated serum uric acid levels should be actively discouraged.

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Declaration of competing interest

Nil.

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