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Treatment of Asymptomatic Hyperuricemia in Chronic Kidney Disease: A New Target In An Old Enemy – A Review

Barse Priti Vinayak B[1] and Prof. More Ashwini B[2]
Student, Pratibhatai Pawar College of Pharmacy, Wadala Mahadev, Shrirampur[1]
Assistant Professor, Pratibhatai Pawar College of Pharmacy, Wadala Mahadev, Shrirampur[2]
Corresponding Author: Barse Priti Vinayak

Abstract: *Chronic kidney disease (CKD) is a severe condition and a significant public health issue worldwide, carrying the burden of an increased risk of cardiovascular events and mortality. The traditional factors that promote the onset and progression of Chronic kidney disease (CKD) are cardiometabolic risk factors like hypertension and diabetes, but non-traditional contributors are escalating.Hyperuricemia, i.e. increased serum uric acid (UA) concentration, is a common problem in clinical practice. While there are clear guidelines concerning management of symptomatic hyperuricemia in acute conditions such as gout, urolithiasis or acute urate nephropathy, less is known about their secondary prevention. Moreover, despite the ongoing debate on the role of Uric Acid (UA) in the pathogenesis of chronic kidney disease, hypertension, cardiovascular disease and heart failure, the management of asymptomatic hyperuricemia in patients with these chronic conditions is still mainly up to physicians' judgement. Individual considerations should always be taken into account when prescribing urate-lowering therapy. In this narrative review study, we attempt to present current trends concerning treatment of patients with either symptomatic or asymptomatic hyperuricemia in the light of the available knowledge on the role of hyperuricemia in the development of gout, renal, cardiovascular and other diseases.*

Keywords: chronic kidney disease; hyperuricemia, uric acid

I. INTRODUCTION

Uric acid is the final product of purine metabolism.Since most uric acid is derived from the metabolism of endogenous purine, eating foods rich in purines contributes only a small portion of the total pool of uric acid. The catabolic steps that generate uric acid from nucleic acids and free purine nucleotides include degradation through the purine nucleotide intermediates hypoxanthine and xanthine. Xanthine is oxidized to uric acid in sequential reactions catalyzed by xanthine oxidase**.(1)** Uric acid cannot be further metabolized and is eliminated through both the gut and the kidneys. Intestinal bacteria degrade one third of total body uric acid, and the kidneys excrete the remaining two thirds. Since only 3% to 4% of uric acid is bound to serum proteins, almost all is filtered at the glomerulus, but 99% of filtered uric acid is reabsorbed from the proximal tubule. This is followed by secretion in the proximal tubules and extensive postsecretory reabsorption, which occurs in the last segment of the proximal tubules**.(2)**

Hyperuricemia is an abnormally high level of uric acid in the blood. In the pH conditions of body fluid, uric acid exists largely as urate, the ion form**.[3][4]** Serum uric acid concentrations greater than 6 mg/dL for females, 7 mg/dL for males, and 5.5 mg/dL for youth (under 18 years old) are defined as hyperuricemia**.[5]** The amount of urate in the body depends on the balance between the amount of purines eaten in food, the amount of urate synthesised within the body (e.g., through cell turnover), and the amount of urate that is excreted in urine or through the gastrointestinal tract. **[4]** Hyperuricemia may be the result of increased production of uric acid, decreased excretion of uric acid, or both increased production and reduced excretion**.[5]**

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Hyperuricemia is defined as a serum uric acid level greater than 7.0 mg/dL, as measured by the automated enzymatic (uricase) method. In boys, serum uric acid concentrations rise at puberty from childhood mean values of 3.5 mg/dL to adult levels of 5.0 ± 2.0 mg/dL. In contrast, levels remain constant in women until menopause, when they begin to rise to the level in men. The normal uric acid level in women is 4.0 ± 2.0 mg/dL. The reason is that estrogen promotes excretion of uric acid during the reproductive period**.(6,7)**

Renal clearance of uric acid is greater in the presence of estrogenic compounds **[8].** Studies have found that males younger than 65 years of age have a prevalence of hyperuricemia four times higher than that of females of the same age. After menopause, serum urate values increase in women to the same values as their male counterparts.

Urate levels have also been found to be increased in chronic kidney disease. The kidneys excrete two-thirds of uric acid produced daily and impaired excretion of uric acid is present in 90% of individuals with hyperuricemia **[9].** The gut eliminates a third of the urate produced daily through colonic bacteria, which almost completely degrades the uric acid with very little left in the stool. This mechanism increases marginally in the presence of kidney failure. 90% percent of filtered uric acid is reabsorbed in the S1 segment of the proximal tubule **[10].** Multiple urate transporters have been found, such as the(urate transporter 1) (URAT1) which is expressed in the apical membrane of the proximal tubule cell and the urate transporter (SLC2A9) (also known as glucose transporter 9), expressed on the basolateral side of the proximal tubule and on the apical membrane in the collecting duct **[11].** Uric acid is secreted rather than reabsorbed in the S2 segment of the proximal tubule and post-secretory reabsorption occurs at a more distal site of the proximal tubule, with 10% of the filtered uric acid appearing in the urine **[12].**

In this pathway xanthine oxidase catalyzes the final oxidation of hypoxanthine and xanthine to uric acid **[13–15].** In contrast to humans, most other mammals possess an additional enzyme in purine metabolism, namely uricase (urate oxidase). Uricaseoxidizes uric acid to 5-hydroxyisourate, and to allantoin, a highly water soluble compound which is most efficiently excreted in urine. Early during the evolution, due to distinct gene mutations, primates have lost uricase activity and the ability to enzymatically produce allantoin. As a result, humans have much higher serum uric acid levels than other mammals and can easily develop hyperuricemia **[16].** Uric acid is a poorly soluble weak organic acid, that circulates in blood (under physiologic pH of 7.40) as urate anion **[13,15,16].** Hyperuricemia may result from an enhanced production or a reduced secretion of uric acid. There is no universally accepteddefinition of hyperuricemia. Preferably, it is defined physicochemically as a serum urate concentration exceeding its solubility point (6.8 mg/dL). Crystals of monosodium urate form at levels exceeding solubility, and they precipitate in joint tissues causing gout.

About two-thirds of uric acid load is derived from internal sources (liver, muscle, intestine) and one-third from dietary sources, including fructose, alcohol, and purine-rich foods like certain meats and seafood **[14].** High fructose intake (e.g. corn-syrup or various soft-drinks) can cause intracellular adenosine triphosphate depletion with enhanced nucleotide turnover and uric acid formation **[17].** Therefore, uric acid lowering treatment almost always includes changes in diet and lifestyle. Kidneys are responsible for most of the daily uric acid excretion (65–75%), with the remaining (25–35%) being excreted through the gastrointestinal tract **[18].** Urate is freely filtered by the glomerulus but, owing to a net proximal tubular reabsorption, its fractional excretion is<10%. Knowledge about tubular handling of uric acid is still evolving and was recently shown to include reabsorption and secretion in the proximal tubule **[19,20],**

High serum uric acid (SUA) levels are closely related to diverse metabolic abnormalities, such as obesity, hypertension, and dyslipidaemia, which are well-established cardiovascular (CV) risk factors**(21).** Previous studies have suggested the potential effect of uric acid on atherosclerosis through vascular smooth cell proliferation and endothelial dysfunction**(22,23).** Although numerous studies have investigated the relationship between SUA and coronary heart disease, the results have been conflicting**(24–28)** Particularly, there is a paucity of data with large sample sizes on the association between hyperuricemia and changes in coronary atherosclerosis. The coronary artery calcium score (CACS) is widely used for cardiovascular (CV) risk stratification in asymptomatic adult populations because of its prognostic value across age, sex, and ethnicity**(29).** Recent data have shown that early

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detection of the presence and progression of coronary artery calcification (CAC) is important in primary prevention**(30,31).**

PATHOPHYSIOLOGY:

Pathophysiology Calculus formation is a complex procedure that include biochemical disturbances of urine stimulating crystal nucleation, aggregation, and probably adhesion. Renal plaques of Randall were demonstrated to play a role in the formation of calcium oxalate but not uric acid calculi by different researches, who examined renal tissue gathered during percutaneous nephrolithotomy **[32,33].** Indeed, urinary irregularities that influence the development of uric acid calculi encompasses constantly low urinary pH (the main factor), hypovolemia and low urinary levels, and hyperuricosuria (explained as daily urinary uric acid exceeding 750 mg/d in females and 800 mg/d in males) **[34,35].**

Persistently low urinary pH

Uric acid urolithiasis is usually associated with persistently low urine pH. Nearly all patients with uric acid calculi demonstrate constantly low urinary pH while the majority excrete normal amounts of urates **[36,37].** On the other hand, patients without congenital or attained conditions to that predispose to formation of uric acid calculi are supposed to have either idiopathic uric acid nephrolithiasis or ‘‘gouty diathesis **[37,38].** Both represents a syndrome of primary gout and exemplified by high serum uric acid, reduced fractional excretion of uric acid, and constantly low urinary pH. Low urinary pH is thought to induce uric acid calculi through basic acid-base chemistry and solubility of the uric acid **[39,40].** Patients with low urinary pH but a regular uric acid secretion may develop uric acid calculi, while others with a standard or increased urinary pH but additional urate secretion will not **41].**

This fact may be demonstrated with the dissociation of uric acid in water. The nitrogen at position N-9 of urate, when dissolved in water, may receive a free proton to develop uric acid. The first acid dissociation constant (pKa) of this reaction is 5.5 pH; the second pKa has no physiological significance. The solubility constant (Ksp) of uric acid is approximately 100 mg/L in aqueous solutions at 37 C, while urate is 20 times more soluble. Urate and uric acid exist in equal proportions at a pH equal to the pKa (Henderson-Hasselbach equation) **[42,43].**Consequently, if 200 mg of urate were added to a 1-L aqueous solution with a pH of 5.5 at 37 C, 100 mg will become uric acid and the remainder will continue to be urate. On the contrary, if 1200 mg of urate were added to an equal volume at a pH of 6.5, 1100 mg will remain in the soluble urate form. These interactions relay on the upward swing of the uric acid dissociation curve at this pH, which plateaus at a pH of nearly 7.2 **[44,45].**

Hyperuricosuria

Hyperuricosuria with regular urinary pH may also result in mixed calculi formation made up of urate and calcium oxalate. Even though urate is most of the times more soluble than uric acid, it can be noted that it is not considerably so. Monosodium urate at high levels precipitates out of solution and is conjectured to result in calcium oxalate crystallization through either; the attenuation of macromolecular inhibitors of lithogenesis, heterogeneous nucleation, and salting-out occurrence. Hyperuricosuria most of the times emanates from nutritional indiscretion, even though mutations in the Urate Anion Transporter 1(URAT1) channel could result in congenital renal hypouricemic hyperuricosuria **[46,47,48].**

Low urinary volume

Diminished urinary output causes increased urinary concentrations of lithogenic solutes. The high concentrations of urate could result in uric acid and monosodium urate precipitation as a result of restricted solubility of uric acid. Consequently, uric acid calculi are prevalent in the tropics and hot environments **[49,50].**

CAUSES:

1.Genetic predisposition: Family history and genetic mutations can increase the risk of developing hyperuricemia **[51].**

2. Dietary factors: Consuming high-purine foods, sugary drinks, and alcohol can raise uric acid levels **[52].**

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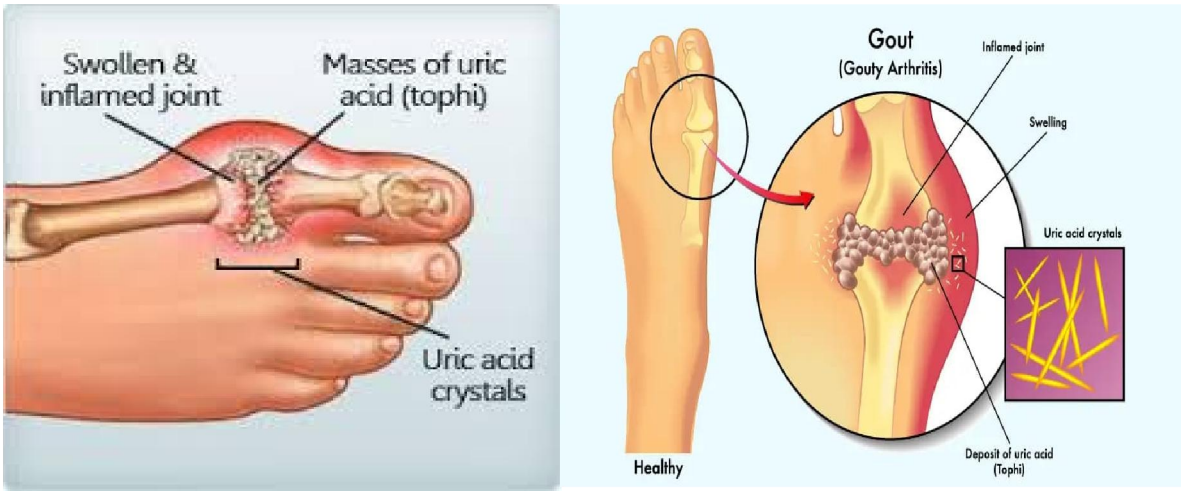
3. Kidney disease: Chronic kidney disease and kidney failure can impair uric acid excretion **[53].**
4. Medications: Certain medications, such as diuretics, beta-blockers, and cyclosporine, can increase uric acid levels **[54].**

RISK FACTORS:
1. Obesity: Excess body fat can increase uric acid production and reduce kidney function **[55].**
2. Age: Uric acid levels tend to rise with age **[56].**
3. Sex: Men are more likely to develop hyperuricemia than women, especially before menopause **[57].**
4. Hypertension: High blood pressure can increase the risk of developing hyperuricemia **[58].**
5. Diabetes: Insulin resistance and diabetes can contribute to hyperuricemia **[59].**

COMPLICATIONS OF HYPERURICEMIA:
Whether complications develop depends on both the level and the duration of hyperuricemia. Major complications include gout, urolithiasis, and acute uric acid nephropathy. However, most people with hyperuricemia never develop symptoms.

Gout :
The incidence of gout increases with age and with the degree of hyperuricemia. In the Normative Aging Study**,(60)** the annual incidence of gout was only 0.1% in people with serum uric acid levels lower than 7.0 mg/dL, rising to 0.5% in people with uric acid levels from 7.0 to 8.9 mg/dL, and to 4.9% with uric acid levels higher than 9.0 mg/dL. In another study**,(61)** patients with serum uric acid levels between 7 and 7.9 mg/dL were followed for 14 years; gout developed in 12%. The initial episode of gout usually follows decades of asymptomatic hyperuricemia. First attacks in men usually occur between the 4th and 6th decades, whereas women experience symptoms after menopause. Although hyperuricemia is generally accepted as the primary risk factor for gout,**(62)** intermittent alcohol abuse, diuretic use, and obesity may contribute to the development of gout in men with asymptomatic hyperuricemia.**(62)**Alcohol may both increase the production of uric acid and impair its excretion.

Gout most commonly affects the first metatarsophalangeal joint. Attacks are typically intermittent; between acute attacks, patients have no symptoms. Chronic tophaceous gout, however, may occur in patients with persistent hyperuricemia, who often have swollen, nodular joints and variable but often persistent pain or stiffness.



Cardiovascular disease
An association between hyperuricemia and cardiovascular disease remains hotly debated, but the data so far do not prove that hyperuricemia is an independent risk factor for cardiovascular disease. High serum uric acid levels are frequently seen in patients with cardiovascular disease, and hyperuricemia may be predictive of an adverse outcome.

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However, proving a direct association is confounded by drug treatments and coexisting conditions such as hypertension and diabetes mellitus that can contribute to high serum uric acid levels**.(63,64).**

Chronic Kidney Disease:

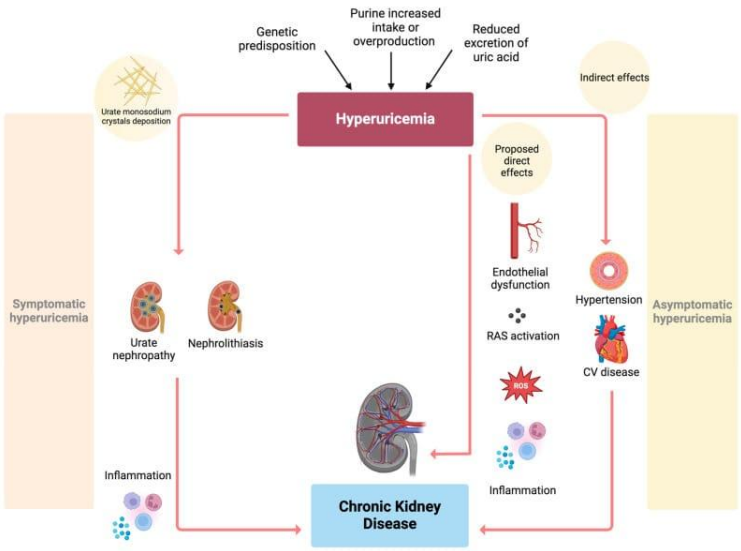
Chronic kidney disease (CKD) represents a growing global health issue. It is an extremely common disease with 850 million people worldwide estimated to be affected **[65,66].** Consequently, the mortality related to this condition is also steadily increasing, and by 2040 Chronic Kidney Disease (CKD) is expected to be the fifth leading cause of death **[67].** This trend is likely due to the rising prevalence and incidence of some conditions like diabetes, hypertension, obesity, and elder age; in fact, the primary etiology of Chronic Kidney Disease(CKD) differs globally, but, especially in high-income countries, diabetes and hypertension are the most common **[68].**

The range of Chronic Kidney Disease(CKD) severity is wide, from mild to advanced forms, eventually leading to end-stage kidney disease (ESKD).Chronic Kidney Disease(CKD) and end-stage kidney disease (ESKD) are also associated with significant comorbidity and reduced quality of life **[69],** and Chronic Kidney Disease(CKD) itself is a well-known, independent risk factor for cardiovascular (CV) events, hospitalization, and death from any cause **[70].** Moreover, kidney diseases, and especiallyend-stage kidney disease (ESKD), are associated with elevated costs of care, with considerable consequences for health systems **[71].**

For these reasons, many efforts have been invested in the last decades in reducing Chronic Kidney Disease(CKD) progression through the implementation of new medications able to slow the renal function decline. Significant benefits have been demonstrated with sodium-glucose co-transporter 2 (SGLT-2) inhibitors in both diabetic and non-diabetic patients **[72-74].**and with non-steroidal selective mineralocorticoid receptor antagonist **[75].**and glucagon-like peptide 1 receptor agonist (GLP1RA) **[76].**in patients with diabetes.

Nevertheless, much remains to be done to limit the progression of renal diseases, and it still crucial to identify the risk factors for Chronic Kidney Disease(CKD) in order to minimize their impact on kidney function decline through prevention and treatment. This concept has been clearly stated in the most recent Kidney Disease: Improving Global Outcomes (KDIGO) guideline for Chronic Kidney Disease(CKD), advocating for an early diagnosis of Chronic Kidney Disease(CKD), especially in high-risk subgroups such as those with hypertension, diabetes, and Cardiovascular (CV) disease and for the implementation of new and existing treatments while optimizing the resources of health systems **[77].**

As a matter of fact, evidence from animal models demonstrates that High Serum Uric Acid (HSUA) levels correlate with endothelial dysfunction and increased activity of the renin-angiotensin system, resulting in arteriolosclerosis and glomerular hypertension **[78,79]**; through analogous mechanisms, elevated uric acid even seemed able to accelerate Chronic Kidney Disease(CKD) progression **[80]** (Figure 1).



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Kidney involvement in hyperuricemia. In the context of symptomatic hyperuricemia (**left side** of the figure), the etiological role of High Serum Uric Acid (HSUA) levels in developing kidney diseases is related to urate monosodium crystals deposition, which can lead to urate nephropathy and nephrolithiasis. In this setting, the crystallized form of uric acid works as an activator of immune responses, triggering inflammation and ultimately causing chronic kidney disease. It has been proposed that the asymptomatic form of hyperuricemia has relevant clinical implications for the kidneys as well (**right side** of the figure). One hypothesis is that High Serum Uric Acid (HSUA) levels may directly affect the kidneys through the pro-oxidative and pro-inflammatory effects of soluble urate, which activates the innate immune system. Moreover, Uric Acid(UA) can induce endothelial dysfunction and increase the activity of the renin-angiotensin system; these proposed mechanisms might eventually lead to arteriosclerosis, glomerulosclerosis, and interstitial fibrosis. In addition to that, Uric Acid (UA) may have an indirect effect on renal function, i.e., by inducing hypertension andCardiovascular (CV) disease, which subsequently cause Chronic Kidney Disease (CKD).

Diagnosis:

Clinical Evaluation

1. Medical history: A thorough medical history is essential to identify potential causes and risk factors **[81].**

2. Physical examination: A physical examination can help identify signs of hyperuricemia, such as tophi or joint inflammation **[82].**

Laboratory Tests:

1. Serum uric acid: Measurement of serum uric acid levels is the primary diagnostic test for hyperuricemia **[83].**

2. 24-hour urine uric acid: Measurement of 24-hour urine uric acid can help assess uric acid excretion **[84].**

3. Kidney function tests: Measurement of serum creatinine and estimated glomerular filtration rate (eGFR) can help assess kidney function **[84].**

Diagnostic Criteria:

1. Serum uric acid levels: Hyperuricemia is typically defined as a serum uric acid level > 6.8 mg/dL (404 µmol/L) in women and > 7.0 mg/dL (416 µmol/L) in men **[81].**

Differential Diagnosis:

1. Gout: Gout is a common complication of hyperuricemia, and the diagnosis of gout can help confirm the diagnosis of hyperuricemia **[85].**

2. Kidney disease: Kidney disease can cause hyperuricemia, and the diagnosis of kidney disease can help identify underlying causes **[84]**

Mechanisms Of Action Hyperuricemia:

Hyperuricemia can result from either increased production or decreased excretion of uric acid. In some cases, both mechanisms may be involved.

A. Increased Production of Uric Acid

This occurs due to:

1. High Cell Turnover:

Conditions such as leukemia, lymphoma, psoriasis, and hemolytic anemia lead to increased nucleic acid breakdown.

Chemotherapy or radiation therapy can cause tumor lysis syndrome, releasing large amounts of purines into circulation.

2. Inherited Enzyme Defects:

Lesch-Nyhan syndrome: Caused by a deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT), leading to impaired purine salvage and excessive de novo synthesis.

Phosphoribosyl pyrophosphate (PRPP) synthetase overactivity: Increases purine synthesis and uric acid formation.

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3. Excessive Dietary Purines:
High intake of red meats, shellfish, alcohol (especially beer), and fructose-rich foods can elevate purine breakdown and urate production.

B. Decreased Excretion of Uric Acid
This is the most common cause of hyperuricemia, accounting for about 90% of cases. It occurs due to:

1. Renal Impairment:
Chronic kidney disease reduces the ability of the kidneys to excrete uric acid effectively.
2. Drugs:
Diuretics (thiazides and loop diuretics), low-dose aspirin, cyclosporine, and pyrazinamide reduce urate clearance by affecting renal tubular handling.
3. Metabolic Conditions:
Insulin resistance (seen in metabolic syndrome and type 2 diabetes) decreases renal urate excretion.
Lactic acidosis and ketoacidosis compete with urate for tubular secretion.
4. Dehydration and Fasting:
Reduce plasma volume and glomerular filtration rate, concentrating uric acid in the blood and reducing excretion**(86).**

Management andTreatment Of Hyperuricemia:
Unlike the other main stone types, UA stones can be managed medically. The aim of the treatment is to increase the solubility of UA in urine and to reduce its concentration.
Increased Fluid Intake
Increasing urine volume to 2.5-3.0 L/day is essential and should be emphasized.
Diet
Protein confers acid and other possible lithogenic factors. The effect is more pronounced in animal than in plant proteins partly as a result of higher acid content per gram of animal protein. Protein restriction raises urinary citrate by acting on the renal proximal tubule. These increased urinary pH and reduced the formation of Uric Acid (UA) lithos. Fruits with high potassium content provide organic anions that will be metabolized to alkali. Alkali in fruits effectively neutralizes the acid load delivered by animal proteins **[87].**

Alcalinization with Potassium Citrate
This treatment creates a urinary environment less conducive to the crystallization of UA by increasing urinary pH and reducing the amount of undissociated UA (Uric Acid). It inhibits urinary crystallization of calcium oxalate by reducing urinary saturation

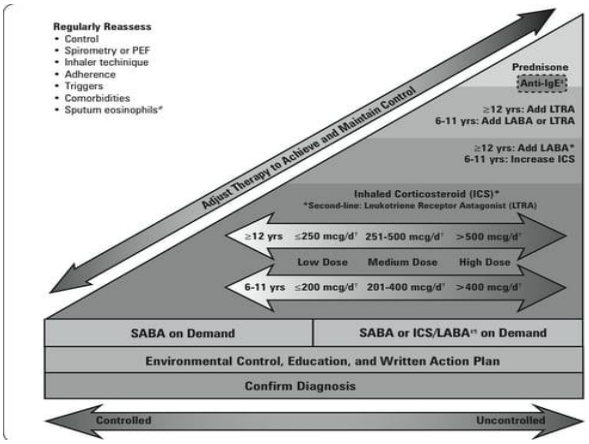

Fig: Hyperuricemia and risk for kidney outcome.

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Treatment of Hyperuricemia

Lifestyle Intervention

It would be optimal that all subjects with hyperuricemia, with or without CKD (Chronic Kidney Disease), in whom treatable secondary etiologies have either been excluded or, if present, appropriately treated, could receive a specific advice with lifestyle measures in order to lower SUA (Serum Uric Acid). Unfortunately, there is a general lack of specific evidence from prospective, blinded, randomized clinical intervention trials that linked consumed quantities of individual dietary components to changes in SUA **[88].** Most of the recommendations are taken from studies of patients with gout and are useful for treating other life-threatening comorbidities of hyperuricemic patients, including obesity, coronary artery disease, hypertension, metabolic syndrome, diabetes mellitus, and hyperlipidemia **[89].** These recommendations may be summarized as follows:

1 Exercise daily and reduce weight. Weight reduction through gradual caloric restriction and exercise can help lower Serum Uric Acid(SUA); nevertheless, the effect of this maneuver is modest (an average weight loss of 7.7 kg over 16 weeks decrease to a mean difference of 1.6 mg/dL SUA in obese patients with gout) **[90].**

2 Limit consumption of purine-rich meat and seafood and consider omega-3 fatty acid supplements with regard to the evidence about higher levels of meat and seafood consumption associated with hyperuricemia **[91].**

3 Limit high fructose corn syrup sweetened soft drinks and energy drinks. Fructose increases SUA given the fact that once absorbed into the cell, unregu-lated phosphorylation of fructose by fructokinase leads to local Adenosine Triphosphate (ATP) depletion and increased Adenoine Monophosphate (AMP) production **[92].** Hypercaloric supplementation with fruc-tose (+35% excess energy) at extreme doses (213-219 g/day) significantly increases Serum Uric Acid(SUA) (mean difference = 0.5 mg/dL). Even isocaloric exchange of fruc-tose for other carbohydrates may be useful for hypertension treatment **[93];** however, this maneuver does not affect SUA in participants from 21 trials **[94].**

4 The consumption of low-fat or nonfat dairy products reduced consump-tion of saturated fat, total fat, and cholesterol has a minimal effect in lowering SUA **[88].**

5 Subjects must limit their intake of beer, wine, and spirits **[88].**

Pharmacological Treatment

Allopurinol

Allopurinol and its major active derived product, oxypurinol, inhibits the xan-thine oxidase and other enzymes involved in purine and pyrimidine metabolism. Oxypurinol is a metabolite that is excreted by the kidney, and therefore, allopurinol requires dose reduction in patients with Chronic Kidney Disease (CKD) **[95].** One reason for caution is the accumulation of xanthine in kidney failure, which will be aggra-vated by the xanthine oxidase inhibitor allopurinol. Allopurinol is not a benign drug and may occasionally precipitate a hypersensitivity syndrome in 2% of pa-tients (Stevens-Johnson-like syndrome) that can be fatal.

To minimize this com-plication, it is recommended to initiate allopurinol at a dose of 50-100 mg/day in subjects with estimated Gomerular Filtration Rate (GFR) less than 30 mL/min/1.73 m^2, increasing the dose to 200 or 300 mg/day every 2-5 weeks to achieve desired UA levels of <6 mg/dL; doses >300 mg/day are permitted so long as they are accompanied by appropriate patient education and monitoring for toxicity (e.g., pruritus, rash, elevated hepatic transaminases) **[88].** Adherence to these published allopurinol dosing guidelines led to suboptimal control of hyperuricemia in most patients **[96].**

Febuxostat

The newer xanthine oxidase inhibitor, febuxostat, is a non-purine urate-lowering drug with more efficiency and specificity for the reduced and oxidized forms of xanthine oxidase than allopurinol **[97].** Febuxostat is metabolized mainly by the liver, has its elimination is primarily through renal and biliary routes, is effective and well tolerated in patients with mild CKD, and appears to be less frequently as-sociated with hypersensitivity or nephrotoxicity; yet the most commonly reported mg/dL, p = 0.03. In this meta-analysis, there were not significant differences with respect the changes in proteinuria or blood pressure, and it was not pos-sible to analyze progression of Chronic Kidney Disease (CKD) in the wake of scarce and heterogeneity of data.

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In another meta-analysis of 19 Renal Contributory Transport Systems (RCTs) enrolling 992 patients with stage 3-5 Chronic Kidney Disease (CKD), allopurinol significantly reduced Serum Uric Acid (SUA) levels, blood pressure, and a small but potentially clinically important and statistically significant improvement in Estimated Glomerular Filtration Rate (eGFR) was noted with a mean difference of 3.2 mL/min/1.73 m² (95% CI from 0.16 to -6.2 mL/min/1.73 m², p = 0.039) **[98].**

Using a different approach, after a group of investigators withdrew allopurinol from subjects with stable Chronic Kidney Disease (CKD), there was an acceleration of Estimated Glomerular Filtration Rate (eGFR) loss in the patients who were not taking angiotensin-converting-enzyme inhibitor **[99].**

Uricosuric drugs

Probenecid and sulfinpyrazone are the most commonly used uricosuric drugs in the United States. Although they are less toxic than allopurinol, their use is limited: they lower serum urate values but also increase the amount of uric acid excreted, thus increasing the risk of nephrolithiasis**.[100]** To obtain the maximum effect from uricosuric drugs, the patient should have a creatinine clearance rate greater than 50 to 60 mL/minute, should drink at least 2 L of fluid daily, and should have no history of urolithiasis or excessive urine acidity.

Ulodesine (BCX4208):

Ulodesine, an inhibitor of purine nucleoside phosphorylase (PNP), operates upstream of xanthine oxidase (XO) in the purine metabolism pathway. By blocking Purine Nucleoside (PNP) activity, ulodesine diminishes the substrates available for xanthine oxidase (XO), thereby reducing uric acid production**.(101)** Currently, this drug is in development for managing hyperuricemia in chronic gout. Promising results have been observed in two Phase II clinical trials, evaluating ulodesine both as a monotherapy and in combination with allopurinol. In a 24-week extension study, the treatment response rates for 5 mg, 10 mg, and 20 mg doses were 40%, 50%, and 45%, respectively, compared to a 25% response rate for the placebo**.(102,103)** Interestingly, no significant adverse events were documented compared to the placebo group. Ulodesine displays no interactions with Cytochrome P450(CYP450) isoforms and undergoes no hepatic metabolism, thereby minimizing anticipated drug interactions. However, there are concerns regarding its potential effects on T cells. Deficiency of purine nucleoside phosphorylase (PNP) has been linked to immunodeficiency and autoimmune disorders**(104).**

Probenecid:

Probenecid is a quintessential uricosuric agent with multifaceted effects on renal function, significantly influencing the elimination of organic anions and tubular reabsorption of urate. Its therapeutic potential extends beyond managing hyperuricemia, demonstrating efficacy as a Urate Transport 1(URAT1)andGlucose Transporter 9 (GLUT9) inhibitor, especially in cases of renal impairment. Probenecid exerts its uricosuric effects by inhibiting renal organic anion elimination and disrupting tubular urate reabsorption. This dual action enhances urinary uric acid excretion, thereby reducing serum urate concentrations. Additionally, probenecid may modulate urate binding by plasma proteins and influence uric acid secretion within the renal tubules **(105).** The comprehensive use of probenecid is not without consideration of adverse reactions, as it spans various organ systems. Gastrointestinal, dermatologic, hematologic, renal, and immunologic manifestations have been reported **(106)**Approximately 5% of users experience manifestations such as rash, gastrointestinal complaints, and hypersensitivity reactions. While serious toxicity is infrequently reported, a notable proportion of patients, approximately one-third, may exhibit intolerance, necessitating discontinuation of probenecid **(107).**

II. CONCLUSIONS

Hyperuricemia is a clinically important factor for the onset of Chronic Kidney Disease (CKD). Many studies have suggested that Uric Acid (UA) itself may harm patients with Chronic Kidney Disease(CKD) by enhancing inflammation and promoting the progression of Chronic Kidney Disease(CKD). Additionally, a high serum UA level may cause kidney damage through a crystal-dependent pathway and non-crystal-dependent mechanisms such as

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inflammation, oxidative stress, and hemodynamic alterations. Most clinical studies have suggested that early treatment of hyperuricemia is beneficial for the control ofChronic Kidney Disease(CKD), Hypertansion (HTN), and other chronic diseases. Because hyperuricemia represents a nontraditional risk factor for Chronic Kidney Disease(CKD), the close association between hyperuricemia and Chronic Kidney Disease(CKD) requires more intensive inquiry.

Several factors contribute to chronic inflammatory status in Chronic Kidney Disease(CKD), including increased production and decreased clearance of pro-inflammatory cytokines, OS and acidosis, chronic and recurrent infections, altered adipose tissue metabolism, and gut dysbiosis.

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