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AN UPDATE ON HYPERURICEMIA - WHEN TO TREAT AND WHEN NOT TO TREAT

Vasantha Kamath[1], Dharani S.*[2]

India.

***Corresponding Author: Dharani S.**

India.

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ABSTRACT

The rising prevalence of asymptomatic hyperuricemia presents a clinical challenge regarding the decision to treat. While guidelines advocate for the initiation of urate-lowering therapy (ULT) in symptomatic hyperuricemia, there is a notable gap in recommendations for managing asymptomatic cases. Given uric acid's involvement in various physiological systems and its role in disease pathogenesis, it is essential to conduct comprehensive studies to develop individualized treatment strategies that optimize health outcomes.

KEYWORD:- Uric acid, Hyperuricemia, Asymptomatic, Gout, Urate-lowering therapy.

INTRODUCTION

India's diverse diet, rich in cereals, pulses, and legumes, face challenges due to westernization, leading to increased consumption of purine-rich foods like organ meats, red meats, processed foods, and sweetened beverages. This shift has contributed to a rise in hyperuricemia, a condition characterized by elevated uric acid levels in the blood, affecting 24% of the population. Hyperuricemia is closely linked to hypertension, diabetes, and gout, with uric acid crystallization causing gout, nephropathy, and nephrolithiasis.

The American College of Rheumatology (ACR) defines hyperuricemia as uric acid levels above 6.8 mg/dl. While gout typically develops in individuals with high uric acid levels, only half of those with hyperuricemia will experience symptoms. ACR 2020 guidelines, conditionally recommended urate-lowering treatment (ULT) for asymptomatic individuals with levels above 6.8 mg/dl, targeting levels under 6 mg/dl.[1]

However, the role of uric acid as both a pro-oxidant and an antioxidant complicates treatment decisions. Elevated uric acid levels may contribute to systemic conditions like cardiovascular disease, chronic kidney disease (CKD), and metabolic syndrome. This has led to growing awareness about treating asymptomatic hyperuricemia, despite the absence of symptoms, to prevent long-term health complications. The debate continues over whether early intervention is necessary for asymptomatic hyperuricemia, with evidence suggesting it may help prevent broader systemic diseases.

History and Hyperuricemia

The earliest records of hyperuricemia and gout dates back to 2640 BC, with the Egyptians describing it as "podagra" and Hippocrates referring to it as "the unwalkable disease" in the late 5th century BC. Galen later identified tophi as monosodium urate (MSU) crystal deposits in cases of prolonged hyperuricemia. Alexander of Tralles was the first to recognize the use of colchicine in treating hyperuricemia. The pathogenesis of hyperuricemia was further elucidated by Antoni van Leeuwenhoek (1632–1723), Garrod, and experimentally supported by Freudweiler, McCarty, and Hollander. Seegmiller and colleagues highlighted excessive urate production and impaired excretion as key causes of hyperuricemia.[2]

An overview on uric acid

Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine and then to uric acid, with normal serum levels ranging from 3.5-7.2 mg/dL in males and 2.6-6.0 mg/dL in females. Uric acid has antioxidant properties, neutralizing singlet oxygen radicals and protecting vitamin C, while also playing a role in neuroprotection and regulating various behavioural functions like sleep, cognition, and mood.

However, uric acid released from necrotic cells acts as a Damage-Associated Molecular Pattern (DAMP), triggering an immune response and the release of pro-inflammatory mediators, which is exacerbated in hyperuricemia. Elevated uric acid also enhances plasma renin activity and up-regulates the renal renin-angiotensin system, contributing to reduced nitric oxide production. High levels promote cellular senescence and

apoptosis, while levels under 5 mg/dL encourage growth factors.[3]

Hyperuricemia arises from a combination of purine-rich food intake, endogenous production, and renal or gastrointestinal under-excretion. Genetic defects in transporters like URAT1, GLUT9, and BCRP can contribute to hyperuricemia, with most uric acid being reabsorbed by the kidneys. Estrogen enhances urate excretion, explaining the higher prevalence of hyperuricemia in men.[4] Additionally, purine degradation increases with age, making older individuals more susceptible.

Hyperuricemia and Its systemic associations

1. Gout is one of the common manifestation of hyperuricemia. It evolves gradually from asymptomatic hyperuricemia persisting for years to monosodium urate (MSU) deposition in cartilage, tendon and around joints and if in sufficient amount triggers acute attacks. MSUs serve as the primary stimuli for initiating, amplifying, and sustaining the innate immune response mediated via NLRP3 inflammasomal complex.

2. Asymptomatic hyperuricemia is linked to an increased risk of hypertension, stroke, atrial fibrillation, and coronary events. However, cardiovascular risk is independent of uric acid levels. Hypertension is farther most commonly associated disease pathology, insinuated postulates like activation of the renin-angiotensin system, inflammatory responses, oxidative stress, vascular smooth muscle cell proliferation, and insulin resistance. Hyperuricemia promotes platelet activation, complement activation, elevated HsCRP, AGE signalling tenures liability to develop atherosclerosis, ASCVD, especially in patients with lower HDL levels.[5]

3. Chronic kidney disease onset and progression is positively associated with hyperuricemia. Kidneys play an important role in excretion of uric acid. Hyperuricemia stems renal inflammation, activation of ACE enzyme, RAAS, impedes eNOS expression steers to renal vasoconstriction and hypertension by compromising renal auto-regulation. Many trials highlighted improvement of eGFR in hyperuricemia patients treated with urate lowering drugs.

4. Urolithiasis and uric acid nephropathy are preventable complications of hyperuricemia, with risk factors including acidic urine pH, oxidative stress, and insulin resistance.

5. Chronic hyperuricemia creates hostile environment to beta cells of pancreas affecting productivity. Inflammation mediated by oxidative stress and insulin resistance have established their routes in beta cell dysfunction, overt diabetes and related metabolic disorders. With increase in serum uric acid by 1mg/dl there is 5% and 9% increase in prevalence of metabolic syndrome in males and females respectively. Uric acid impels adipogenesis, hypertriglyceridemia, low HDL and fat accumulation leading to central obesity and insulin resistance.[6,7]

6. In pregnancy, hyperuricemia predisposes to hypertensive disorders and foetal complications, such as IUGR.[8]

7. Among people living with HIV, hyperuricemia is common and linked to disease activity and antiretroviral treatment.

8. Drug-induced hyperuricemia has been observed with cyclosporine, thiazides, pyrazinamide, ethambutol, levodopa, theophylline, didanosine etc. It has also been seen with favipiravir which was used in the treatment of COVID-19.[9]

Diagnosis of hyperuricemia

1. Serum uric acid analysis: it should be done after overnight fasting. Avoid smoking, alcohol, strenuous exercise, and medications that impair uric acid metabolism from the night before the test.
2. When to use 24-hour urine uric acid estimation: in patients with recurrent nephrolithiasis, early-onset gout, or a strong family history of hyperuricemia. It helps differentiate between over-production or under-excretion of uric acid.
3. Ultrasonography for diagnosis: can detect features of local inflammation, erosions, and urate crystal deposition. “Double contour sign” - a hypoechoic crystal band over hypoechoic joint surface cartilage. It can also reveal chronic gout features such as: Punched-out lytic lesions, tophi, spiky periosteal appositions.
4. Conventional CT and MRI is rarely used in the diagnosis of hyperuricemia or gout.
5. Synovial fluid analysis is indicated if the diagnosis remains uncertain.

To treat or not to treat: Management of asymptomatic hyperuricemia - As per Integrated Diabetes & Endocrine Academy (IDEA) consensus statement

I. Indications for drug therapy (IDEA Consensus 2019): pharmacologic intervention is considered for asymptomatic hyperuricemia when:

1. SUA levels exceed 9 mg/dL.
2. SUA levels are between 7.0-8.9 mg/dL in the presence of co-morbid conditions such as renal stones or chronic kidney disease (CKD) stage III (eGFR < 60 mL/min/1.73m²).[10]

II. Lifestyle modifications: patients with asymptomatic hyperuricemia should first be advised to make lifestyle changes, including weight reduction,

alcohol cessation, and avoidance of purine-rich animal-based foods, to maintain serum uric acid levels < 6.5 mg/dL.

A. Purine-rich foods: legumes, meat extracts, organ meats (brains, kidneys, liver, sweetbreads), roe (fish eggs), sardines, yeast.
B. Moderate-purine foods: asparagus, fish, meat, mushrooms, peas (dried), shellfish, spinach
C. Low-purine foods: bread, butter, cereals, cheese, chocolate, coffee, eggs, fruit, milk, noodles, nuts, olives, rice, salt.

First-Line treatment

Allopurinol (Xanthine Oxidase Inhibitor): initiate with low dose 50 to 100mg/dl to titrate till desired serum uric acid achieved. It is the preferred agent for reducing uric acid production. Common side effects include hypersensitivity reactions (e.g., Steven Johnson syndrome, toxic epidermal necrolysis), gastrointestinal issues (e.g., loose stools), headaches, itching, and rashes.

Caution is required in patients receiving immunosuppressive drugs (e.g., azathioprine, 6-mercaptopurine), as allopurinol increase their half-life, potentially leading to toxicities.

There is increased risk of skin reactions when combined with ampicillin or amoxicillin.

Pre-treatment recommendation: FDA advises testing for HLA-B*58:01 before initiating allopurinol to minimize the risk of severe hypersensitivity.

Second-Line treatment

Febuxostat (Xanthine Oxidase Inhibitor): is indicated when allopurinol is not tolerated or when target uric acid levels are not achieved with allopurinol.
Initial dosage: 40 mg/day, It is the preferred choice for patients with CKD to prevent gout and slow disease progression.

FDA warning (2017): The CARES trial identified an increased risk of cardiovascular events associated with Febuxostat, leading to a safety warning.[11]

Other treatment options

1. Probenecid: are commonly used uricosuric drugs, but their use is limited by the risk of nephrolithiasis. To optimize their effectiveness, patients should have a creatinine clearance >50-60 mL/min, drink at least 2 liters of fluid daily, and have no history of urolithiasis or excessive urine acidity.[12]

2. Lesinurad (Selective URAT1 Inhibitor): a uricosuric agent that reduces serum uric acid by inhibiting its reabsorption in the kidneys. Typically prescribed in combination with allopurinol or Febuxostat in cases refractory to monotherapy. It is associated with cardiovascular risks and nephrotoxicity.

3. Verinurad: another URAT1 inhibitor in clinical trials has nephrotoxicity concerns.

4. Aspirin: at high doses (4-6g/day), aspirin can promote uric acid excretion, although at low doses it increases reabsorption, rendering it impractical for managing hyperuricemia.

Certain medications though not primarily designed for gout, exhibit urate-lowering effects and may be considered in the presence of coexisting conditions[13]

1. Anti-hypertensives: ARBs, CCBs.
2. Anti-diabetics: Metformin, SGLT-2 inhibitors.
3. Lipid-lowering agents: Fibrates, HMG CoA reductase inhibitors.
4. Anti-obesity drugs: Sibutramine, Orlistat.

Prophylactic treatment of hyperuricemic patients are indicated in conditions as mentioned in Table 1.

Table 1: Indications of prophylactic treatment in hyperuricemia.

Conditions of extensive cell lysis, for example patients receiving chemotherapy/radiotherapy
History of gouty flares
Moderate impairment of renal function
Patients prone to future attacks of gout
Asymptomatic familial hyperuricemia
Patients with recurrent uric acid stones
Evidence of tophi on ultrasound
Chronic gouty arthritis
Binge alcoholics
Patients with severe hyperuricemia (SUA>12mg/dl in males and >10mg/dl in females)
Urinary uric acid excretion > 1gm/24hours

Step ladder approach for high cardiovascular risk patients (updated 2023 Cardiology journal)

Step 1: diagnose hyperuricemia if SUA levels >6mg/dl or >5 mg/dl in high CV risk.
Step 2: assess co-morbidities, discontinue medications that elevate uric acid levels.
Step 3: educate patients on lifestyle modifications, exercise, ensure adherence to treatment.
Step 4: initiate allopurinol at a dose of 100-200 mg/day titrate 300-600mg/day, max 900mg/day, to reach SUA <6mg/dl or <5mg/dl in high CV risk patients.

Step 5: consider combination therapies if required and monitor serum uric acid twice a year.[14]

CONCLUSION

Hyperuricemia now extends beyond gout and renal stones, necessitating updated guidelines. The target for urate-lowering therapy should be <6 mg/dL, but levels <3 mg/dL are not recommended due to potential links to neurodegenerative diseases such as Parkinson's, Alzheimer's, and motor neuron disease. Although IDEA consensus highlights optimal treatment modality for asymptomatic hyperuricemia, maximum drug dosage and duration remains uncertain.

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