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Management of asymptomatic hyperuricemia at primary care

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Abstract
Asymptomatic Hyperuricemia (AHU) is a condition with abnormal serum uric acid levels, without clinical signs or symptoms. AHU is a risk factor of various clinical conditions as hypertension, renal diseases, metabolic syndrome, stroke etc. It is controversial that AHU should be treated with Uric acid lowering therapy (ULT), and most of the latest guidelines do not suggest the use of ULT. However, non-pharmaceutical measures can help in management of this condition.

Keywords: Asymptomatic, hyperuricaemia, AHU, ULT

Introduction
Prevalence of hyperuricemia is around 13-21% in general population and thought to be due to the change is life style (dietary habits, lake of exercise, and increased use of alcohol) and higher in adult males, this could be due to the protective effects of estrogen compound in females, which enhance the renal clearance of uric acid [1-3]. Individuals with hyperuricemia have 2.7 folds higher risk of developing hypertension (HTN), 1.6-fold for dyslipidemia, 3.2 folds for obesity, 2 folds for chronic kidney disease (CKD) and Diabetes Mellitus (DM) within 5 years [4]. It is estimated that 2/3rd individuals with asymptomatic hyperuricemia remains symptoms free throughout their lives, and only 1/3rd have a chance of having symptoms [5].

Definition
Asymptomatic Hyperuricemia (AHU) is defined as abnormal serum uric acid levels in absence of any clinical signs or symptoms of monosodium urate crystals deposition, such as gout or nephrolithiasis. Cutoff value of uric acid levels varies from 6.1-7mg/dl and European League against Rheumatism (EULAR) recommends the cutoff value of 6.0mg/dl [6, 7].

Pathophysiology
Uric acid is the end product of purine metabolism, and Xanthine oxidase is the enzyme which catalyzed xanthine into uric acid. One third of total body uric acid is degraded by gut bacteria, and the rest 2/3rd is exerted by kidneys. The high levels of uric acid exceed the capacity of solubility, and has a potential to cause intracellular and mitochondrial oxidative stress, reduction of bioavailability of nitric oxide to endothelium, leading to endothelial damage and stimulation of renin angiotensin system.

Causes
It is due to increase dietary intake, increased synthesis or reduced excretion.

A. **Decrease Urate excretion:** Hypertension, Drugs (low-dose salicylate, ethambutol), Lead nephropathy, Chronic kidney disease.
B. **Increase Urate overproduction:** High purine diet (red meat, seafood, high consumption of bear, spirits, sugar or fructose sweetened soft drinks are the main risk factors for high uric acid concentration), psoriasis, myeloproliferative disorders, and vigorous muscle exertion.
C. **Combined (under excretion and overproduction):** Primary (idiopathic) & secondary hyperuricemia, G6PD deficiency, tissue hypo perfusion, alcohol consumption.

Complications
Hyperuricemia can result in both crystal deposition and non-crystal deposition disorders, depending upon the urate levels, genetic and environment factors. Crystal deposition disorders include; Gout, CKD and nephrolithiasis. Non-crystal deposition includes; HTN,

CKD, Cardiovascular diseases, obesity, insulin resistance and metabolic syndrome [8].

Risk of Gout increase with high uric acid level >10 mg/dl in about 30-49% of cases while risk is lower with uric acid level of 6.0-6.9mg/dl (0.6%) and < 6.0mg/dl (0.5%) [9].

Studies found that genetic or environment factors rather than only the urate levels play a role in gout development, including the factors which inhibit or facilitate the formation of MSU crystals in tissue at high urate levels [10].

A meta-analysis showed hyperuricemia is independent risk for kidney disease in patients with normal baseline renal function. It is also estimated that HTN plays a major role in proceeding to chronic kidney disease among hyperuricemia patients [11].

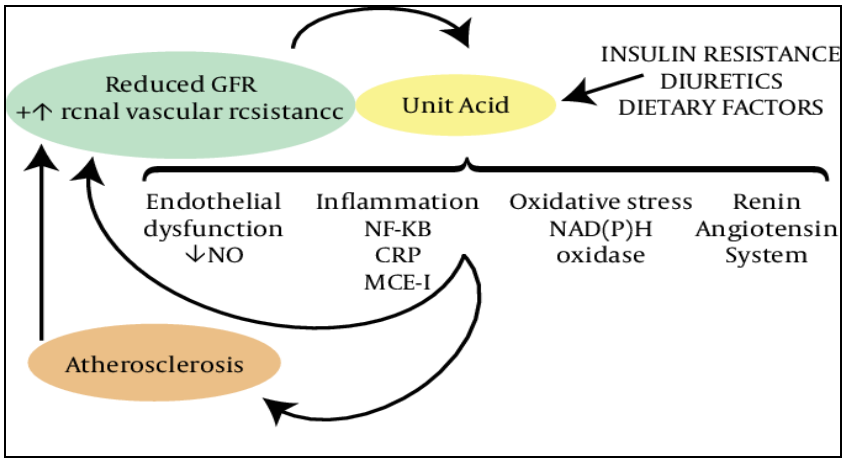

Fig 1: Associations between Hyperuricemia and Chronic Kidney Disease

There is a significant association of urate levels with CVD as other comorbids. Coronary artery calcification is more severe in those patients with AHU and articular MSU deposits found by ultrasound as compare to without crystal deposition or abnormal urate levels [12].

It is estimated that each 1.0mg/dl rise in serum urate level was related with 30--50% increase in risk of metabolic syndrome while 6-11% increase in risk of Type2 DM [13, 14].

Diagnosis

AHU is diagnosed by chance during routine investigations. Most patients remain asymptomatic so it is important to sort out only those individuals, who are at risk for damage from high urate levels and can have benefit from urate lowering therapy (ULT) [15]. Musculoskeletal Ultrasound and detect the crystal deposition in joints and soft tissue long before the appearance of gout. These crystals later proceed to the articular symptoms and called has hidden gout. It is estimated that 13% of the AHU patients have modification of first metatarso-phalangeal joint identified by ultrasound in contrast to only 7% of normal population [16].

- 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

Management

Most of the guidelines do not suggest the treatment for AHU, due to the fact that it rarely proceed to gout. Treatment includes.

Non pharmacological

a. Healthy diet (fruits, vegetables, nuts, low fat dairy products, legumes, whole grain, low salt, and avoidance of soft drinks, red meat and processed meat), reduction in alcohol intake and use of vitamin C supplements 500-2000mg/d (It should be avoided in those with history of oxalate renal calculi). These dietary changes can reduce the urate levels 1.0-1.3mg/dL in those with baseline urate was above 6.0- 7.0mg/dL respectively [17].

b. Weight Loss: It is estimated that >5kg loss of weight is related with reduction in urate levels by 10.0-8.0 umol/dl [18].

c. Physical activity not only reduce urate levels but also reduce triglycerides levels and insulin resistance. Regular physical activity for 150 mins per week or 30 minutes per day for 5 days per week can reduce the mortality rates by 11% in patients with hyperuricemia [18].

Pharmaceutical management

According to European League against Rheumatism (EULAR), British Society of Rheumatology and American College of Rheumatology, pharmaceutical treatment is not recommended for AHU. However, the Japanese Society of Gout and Nucleic Acid Metabolism recommends the ULT in AHU patients whose urate levels are >8.0mg/dl. It is found that allopurinol is associated with various side effects including skin allergies (0.5% in new users, 0.2% admissions and 0.04% deaths). Similar studies found the adverse outcome including CVD events, nonfatal MI, nonfatal stroke was found in 10.8% of those taking febuxo stat and 10.4% of those taking allopurinol.

The other pharmaceutical agents which are related with raised serum uric acid levels should be avoided, as beta-blockers, ACE inhibitors, ARB other than losartan, diuretics

and low dose aspirin. In contrast the drugs which help in renal excretion of uric acid should be encouraged as fenofi brate, atorvastatin for dyslipidemia, Losartan or CCB for HTN, biguanides and glitazones and iSGLT2 for diabetes, clopidogrel can be used in place of aspirin, and among diuretics, spironolactone can be used when possible [20].

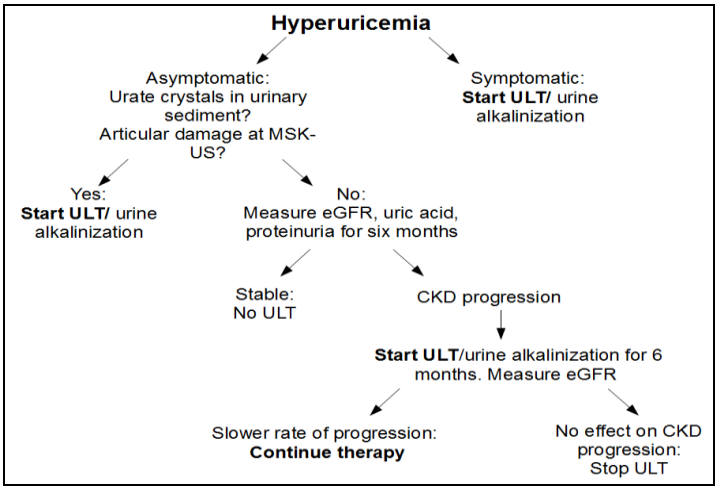

Fig 2: Urate-Lowering Agents in Asymptomatic Kidney Blood Press Res 2018; 43:606-615

Conclusion

The use of ULT for AHU is not recommended, however the risk factors related with AHU should be treated accordingly. The non-pharmacological measures are underestimated, although they are found beneficial.

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