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Prehyperuricemia: New Milestone in Metabolic Disorders

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ABSTRACT

The global population is living amid a metabolic explosion. The prevalence of hyperuricemia, as a metabolic disorder and a causal agent of non-communicable diseases, has been gearing up rapidly worldwide during the last two decades due to consuming a high purine diet, alcohol, red meat, high fructose-containing food, and lifestyle changes. The invisible bond between hyperuricemia and many non-communicable diseases is more robust than before. During the evolution of hyperuricemia, systemic inflammation develops, leading to endothelial dysfunction and end-organ injury. These molecular changes were not recognized previously. Hyperuricemia is now a metabolic, more clearly a vascular disorder than a crystallization disease. Asymptomatic hyperuricemia is no more benign, and gout is not synonym with hyperuricemia or vice versa. Diagnose hyperuricemia in an early stage at a high normal level and control it to prevent the development and complications of many hyperuricemia-related extra-articular diseases. For more acceptance and importance, this high normal level of serum uric acid can be named prehyperuricemia. As in the case of prediabetes and prehypertension, prehyperuricemia should be diagnosed early irrespective of age and sex; preventive measures have to be taken and maintain uric acid at a safer level.

Keywords: Serum uric acid, hyperuricemia, prehyperuricemia, high normal value of serum uric acid, metabolic disorder, non-communicable disorder, and molecular mechanism.

INTRODUCTION

Uric acid (UA) is a weak acid and the end product of purine metabolism in humans. The prevalence of hyperuricemia (HU) increased double or even triple during the last two decades globally. Recent epidemiological studies have clearly shown that HU has a linear relation with non-communicable diseases (NCDs) and many other conditions. The pathophysiology involved in HU includes oxidative stress, endothelial dysfunction, and end-organ damages. Various studies have shown that the underlying molecular changes induced by HU start even before the present cutoff value of 7mg/dL. However, it is uncertain when and above which level of UA these changes start and become one of the causal factors for NCDs. Today NCDs are the leading causes of morbidity and mortality in the entire world. Numerous clinical studies have shown that a reduction in serum uric acid (SUA) can prevent the development of many NCDs and their complications. Hence, it is advisable to screen HU early and prevent metabolic issues. The introduction of new metabolic terminology prehyperuricemia (pre-HU) may be appropriate. Complications of HU take many years to develop. By increasing

awareness and screening at this high normal value of UA, the development of symptomatic HU or asymptomatic HU with many NCDs can be prevented. Manage pre-HU with non-pharmacologic measures like lifestyle modification and improve the quality of life.

Search Strategy

Articles were referred in Google search and pub med, from 1965 to 2021 using keywords uric acid, hyperuricemia, high normal value of SUA, metabolic disorder, non-communicable disorder, molecular mechanism, and preventive measures. This article highlights the explosion in the prevalence of HU, their molecular relations with NCDs and many other diseases, the importance of early screening for HU, and its management

Definition of Hyperuricemia

Hyperuricemia is defined as serum uric acid level of more than 7 mg/dL in men and 6mg/dL in women on a physiochemical basis. The commonest complication of HU was gout until a few decades ago, but it is slowly changing to metabolic disorders. The incidence of gout in the HU population is only less than 9%. Hence, HU need not always be symptomatic. Asymptomatic HU is more dangerous as it leads to endothelial dysfunction, oxidative stress, insulin resistance, macrovascular, and microvascular complications silently-a classical iceberg phenomenon. Thus high UA imposes detrimental effects on almost all systems. Why are all HU patients not necessarily suffering from gout? HU is a metabolic disorder, and systemic inflammation is the primary pathology; as these progresses, it may affect joints to develop gout only when the physiological environment favours it. The present cutoff value of 7mg/dL of HU was composed and periodically edited on a physiologic basis only. The threshold of UA level increased total mortality at 4.7 mg/dL and cardiovascular mortality at 5.6 mg/dL risk, which was significantly lower than the clinical diagnostic value of 7 mg/dL. On a metabolic basis, it is advisable to lower the cutoff value below 7mg/dL in men and below 6mg/dL in women or give more importance to SUA at a high normal value, as HU is now concerned with the metabolic disorder than articular crystallization.

Definition of Prehyperuricemia

Prehyperuricemia (pre-HU) may define as a metabolic condition where serum uric acid value is at a high normal level between 6-7 mg/dL in men and 5-6mg% in women. This value is presently considered as normal or high normal. At this level or even below this, UA-induced systemic inflammation develops. (Flowchart.1)

History

Humans have lost the capacity of degrading UA by the enzyme uricase during evolution over 15 million years ago by mutation [(1)]. Gout is one of the oldest diseases and was named in 1200 AD. Even though UA was identified two centuries ago, the exact pathophysiology of hyperuricemia is not known clearly. In the present generation, the mean serum UA level is slowly increasing. A study from the US reported that the mean SUA levels rose from less than 3.5 mg/dL to 4.2 mg/dL between the 1920s and 1940s. However, during the 1950s to 1980s periods, the magnitude of SUA hike was more, from 5.0 to more than 6.0mg/dL [(2)].

The journey of HU from crystallization diseases to metabolic disorders was fast in the last two decades. HU was connected with gout and nephrolithiasis only, but nowadays it has been identified as a major risk factor and biomarker of many metabolic and hemodynamic abnormalities. The century-old hyperuricemia is no more benign but a silent killer.

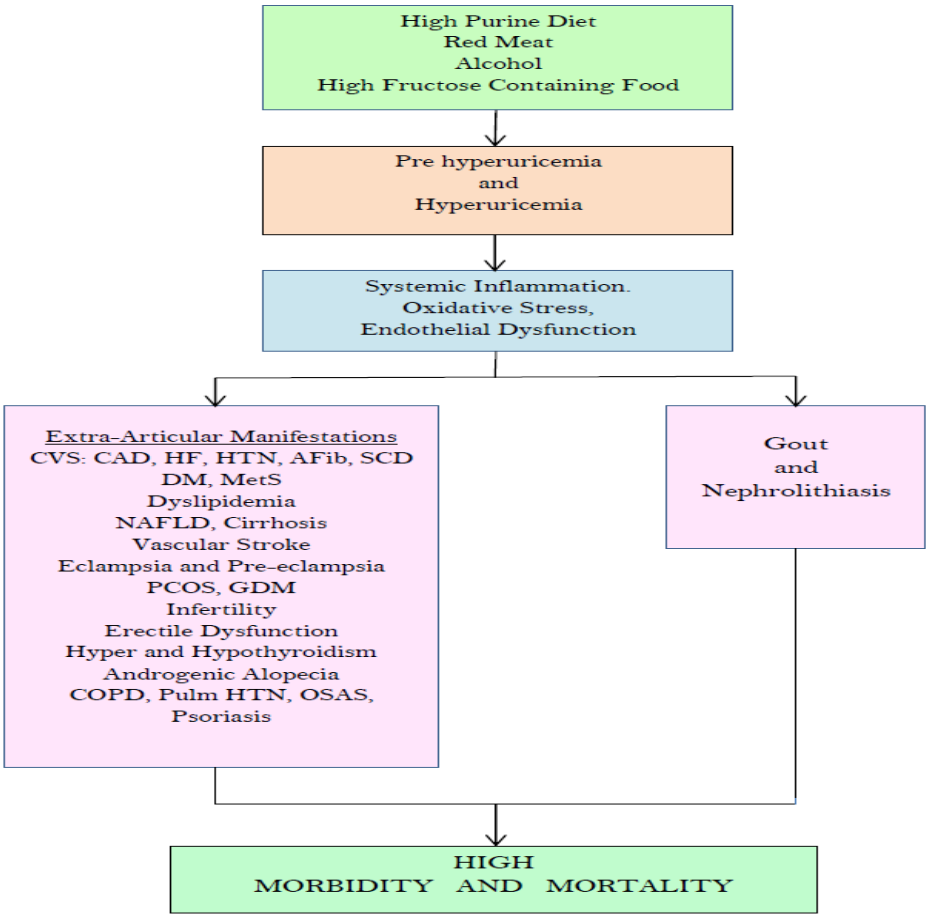

Figure-1. Flowchart: Impact of Hyperuricemia in Human

SCD: sudden cardiac death, AFib: Atrial fibrillation, MetS: metabolic syndrome, PCOS: Polycystic ovarian syndrome, GDM: gestational DM, OSAS: obstructive sleep apnoea syndrome, NAFLD: non-alcoholic fatty liver disease, COPD: chronic obstructive pulmonary disease, HF: heart failure.

Epidemiology

At present HU is the second most metabolic disorder after diabetes mellitus [(3)]. As the lifestyle of the present generation changed severely due to the consumption of a high purine diet, red meat, alcohol, and high fructose-containing foods, the prevalence of HU has become the fourth highest NCD after hypertension, diabetes mellitus, and dyslipidemia[(4)]. The prevalence of HU has increased twice or thrice in the last two decades globally. In some populations, its prevalence has gone up to 85%, which is on the surge [(5)]. The prevalence was 170 million in China and 32.5 million in the United States during 2019 [(6, 7)].

Uric Acid-Induced Molecular Mechanism

UA is the most abundant and powerful antioxidant in humans. However, UA expresses a pro-oxidant effect at higher concentrations [(8)]. UA is a double-edged sword. This paradox could be an antioxidant effect in the extracellular environment (primarily in plasma) or pro-oxidant at the intracellular level (primarily within the cell). UA act as an antioxidant up to 4.7mg/dL level only. When uric acid enters the cells mediated by specific organic anion transporters, it induces an oxidative cascade that has been shown in vascular smooth muscle cells, endothelial cells, adipocytes, islet cells, renal tubular cells, and hepatocytes. HU is connected with the occurrence and development of NCDs by regulating molecular signals, like an inflammatory response, oxidative stress, insulin resistance, endothelial dysfunction, and endoplasmic reticulum stress, even before pre-HU [(9-13)].Also, when UA enters vascular cells and adipocytes, it induces a

pro-oxidative effect by activating the NADPH oxidase system and stimulating mitochondrial oxidative stress [(14)]. The markers of systemic inflammation like leukocyte count, C-reactive protein, and inflammatory cytokines such as interleukin-6, IL-1RA, IL-18, tumor necrosis factor-α may increase in HU and pre-HU [(15)]. Researchers have linked HU and pre-HU with systemic inflammation [(16)]. Today, part of the uric acid debate, the question is `chicken or the egg first ?` hyperuricemia – insulin resistance – hypertension, Jesse in his article, clearly shows that the relationship between UA and insulin resistance is unidirectional and hyperuricemia comes first and later these two lead to hypertension[(17)] . The mean value of uric acid is slowly increasing(6-6.5mg/dL) in the entire world population, and by the time it crosses high normal value, adverse molecular and inflammatory mechanisms might have started, which in turn leads to NCDs and end-organ damages. Reduction in SUA improves the markers of systemic inflammation, NCDs, and its complications [(18-20)]. Hyperuricemia and high normal uric acid level strongly suggest the presence of low-grade systemic inflammation even without gout [(15)]. UA-induced systemic inflammation may be the mechanism by which it contributes to the development of NCDs even in the absence of gout [(21)].

Hyperuricemia Associated Extra-Articular Diseases

1. UA and Cardiovascular Disease

UA is a modifiable and independent risk factor for CVD, especially in patients with comorbidities. High SUA levels progressively associated with sudden cardiac death (SCD) and cardiovascular mortality (CVM) [(22, 23)].

1.A. HYPERTENSION

In 1966, it was reported that 47% of hypertensive patients were hyperuricemic [(24)]. Currently, UA is a biomarker of HTN. Increasing SUA levels by 1 mg/dL results in a 13% hike in incident HTN [(25)]. Approximately 25-40% of patients with untreated HTN and more than 80% of patients with malignant HTN have high SUA levels [(26)]. SUA emerged as one of the strongest and independent risk factors for prehypertension, which later progresses to hypertension [(27)]. This progression from prehypertension to hypertension incidence is more than 20% over five years in hyperuricemic people compared with the normouricemic group and it highlights the influence of UA in prehypertension [(28)]. Besides, this study highlights the importance of managing hyperuricemia at the prehypertensive stage. SUA is strongly and independently associated even with nocturnal non-dipping of HTN [(29)]. Recently, reports coming with urate-lowering therapy results in the reduction of blood pressure in adolescents [(30)].

1. B. ATHEROSCLEROSIS

UA is a risk factor for atherosclerosis. HU causes atherosclerosis in macrovascular beds and microvessels of major organs. Young adults with HU show coronary artery calcification, and even high normal value is a risk factor for subclinical atherosclerosis. SUA may increase the pulse wave velocity, escalate arterial stiffness from 6.2mg/dL, and accelerate vascular aging [(31)].

1. C. CAD

UA is a marker and risk factor for acute coronary events. The overall risk of CAD mortality increases by 15% for an increase of 1mg/dL of SUA [(32)]. Xiao et al. brought out the relation between SUA and young CAD below 45 years. SUA is likely to increase the aortic pressure and aortic stiffness [(33)].

1. D. AFib

Hyperuricemia is a novel marker for atrial fibrillation, both in chronic and paroxysmal. UA level has an independent association with AFib with or without co-

morbid, and the higher the serum level, more the chance of AFib [34].

1. E. HEART FAILURE

The risk of heart failure increase by 20% for every 1mg/dL increase of SUA [35]. HU in heart failure may be due to the up-regulation of the xanthine oxidase, increasing the risk of heart failure by 65%.

2. UA and Metabolic Syndrome

A quarter of the adult population in the entire world suffers from metabolic syndrome (MetS). Choi et al. report that up to 60 % of MetS were hyperuricemic [36]. More clearly, the third national health and nutrition examination survey reported the prevalence of metabolic syndrome at various levels of SUA. MetS starts even below the level of 6mg/dL of SUA. This study has shown a linear increase of MetS with the rise of SUA and recommends considering HU as a criterion of MetS and treating it early to prevent complications [36]. Presently, HU is a marker for early diagnosis and prevention of MetS [37]. Maintaining SUA at a lower level may avoid the burden of MetS [20].

3. Diabetes Mellitus

A population-based study was reported UA as a solid and independent risk factor for T2DM [38]. The diabetogenic action of SUA was reported in 1950 [39]. The risk of developing T2DM increases by 15-20% for every 1mg/dL increase of SUA independent of comorbidities [40]. The future risk of developing T2DM is directly proportionate to the level of SUA, irrespective of age. Another study reported that the high normal value of SUA (UA 5-6 mg/dL) is associated with a marked increase in the development of DM in women compared to low normal SUA in the study group. At the same time, men were at SUA level 6-6.8mg/dL for diabetic risk [41].

4. UA and Lipid

Serum total cholesterol, LDL cholesterol, and especially triglyceride is directly associated with SUA levels, but HDL cholesterol is inversely related [42].

5. UA and Kidney

SUA is a marker of CKD and acute onset renal disease. Various studies have shown that a high SUA level is associated with longitudinal decline in GFR and worsening renal function. High SUA is associated with a reduction in the number of nephrons, renal tubular atrophy, and hence low GFR [43, 44]. When the SUA is lowered, there is an attenuation of albumin excretion and a slowdown of the eGFR decline in people with T2DM [45]. In T2DM, a high normal SUA level might predict CKD development even in preserved renal functions. Urate lowering therapy decreases inflammation and slows down renal disease progression even in patients with moderate CKD [46]. A study by Kanbay reported that UA lowering might slow down the progression of renal disease in hyperuricemic populations, and there were improvements in renal function by treating asymptomatic HU [47]. Moreover, another study by Siu noticed that the treatment of asymptomatic HU delays the progression of renal disease [48]. SUA is an independent risk factor for CKD, even in the absence of T2DM [49]. Renal dysfunction in T2DM starts even at SUA level 6.3mg/dL (high normal value) and carries a poor prognosis [50].

6. UA and Liver

Non-alcoholic fatty liver disease is the commonest cause of liver function abnormality, and it affects more than 20% of people globally [51]. The relationship between SUA and NAFLD was first described in a small Italian study in 2002(52). Every 1 mg/dL SUA level increment led to a 21% increase in the NAFLD risk [53]. Uric acid lowering may be one of the aims in preventing NAFLD [54].

7. UA and Brain

7 A. STROKE

The pro-oxidant neurotoxic effect of UA may negatively affect acute stroke. A Higher SUA level shows an increased stroke rate and mortality [55].

7. B. DEMENTIA

UA is high in vascular or mixed dementia[56]. Meanwhile, UA as an antioxidant has a neuroprotective role in Alzheimer's disease and Parkinson's disease. Hence UA should not be reduced to hypouricemia level (SUA below 2.5mg/dL).

8. Other Associated Disorders

SUA may be high in COPD and higher the value higher the mortality [57]. In acute respiratory distress syndrome, the SUA level is on the higher side, and it has a prognostic role. In hyperthyroidism, HU is due to higher BMR and elevated urate production. However, in hypothyroidism, HU is due to decreased renal blood circulation. High levels of SUA were detected in patients with psoriasis and chronic dermatitis. Younger males with high SUA levels are associated with androgenic alopecia [58]. SUA level is higher in women with the polycystic ovarian syndrome. In 1917 Slemons and Bogert first noticed that UA was elevated in pre-eclampsia/eclampsia, and elevated UA is now recognized as a stable biomarker in these conditions [59]. An increased level of SUA in pregnancy may also lead to the development of gestational DM (GDM) by 4%. HU may be a marker for an increased risk of erectile dysfunction (ED) and male infertility. Each 1 mg/dL increment in SUA level is associated with a twofold increased risk of ED [60]. Ocular abnormalities like retinopathy, dry eye syndrome, red-eye, uveitis, glaucoma, and cataracts are associated with high UA [61]. High salivary UA is associated with periodontitis and recurrent aphthous ulcer.

Life Span

According to a new study by researchers at the University of Limerick's School of Medicine, high values of serum uric acid can reduce lifespans by up to 11 years for men and six years for women [62].

DISCUSSION

Non-communicable diseases have become the leading cause of morbidity and mortality. It kills 41 million people yearly, equivalent to 71% of all deaths globally, and is an epidemic now. Meanwhile, there is an exponential increase in the prevalence of hyperuricemia in the entire world. Recent works of literature quoted that HU is linked not only to cardio-reno-metabolic disorders but many more to add to this list. HU is not synonymous with gout. The association between NCDs and hyperuricemia has become more pronounced in recent years and goes hand in hand. HU may be symptomatic or asymptomatic; this UA debate was two decades ago. Today HU is more of a metabolic disorder than a crystallization disease. Uric acid has recently regained clinical interest and popularity based on emerging data suggesting the causative role of hyperuricemia in NCDs and many other conditions. It is time to change the term asymptomatic hyperuricemia; it is a killer disease now. The detrimental effect of hyperuricemia starts even earlier than the HU value of 7mg/dL. The incompletely explained and invisible relationship between uric acid and diabetes has gradually become a hot topic for researchers, making them more straightforward now. Does uric acid have a causal role in developing NCDs mediated by systemic inflammations? The answer is yes, as numerous recent studies have shown that a reduction in SUA reduces inflammatory markers.

In gout and even patients with tophi, uric acid may be normal. All hyperuricemia is not symptomatic, and all gout patients are not hyperuricemic. However, there can be systemic inflammation in both these groups of people. Hyperuricemia is not gout equivalent or vice versa and is a metabolic disorder. Gout is one of the few clinical manifestations of hyperuricemia, which is painful, whereas other significant groups are

painless and comfortably categorized as asymptomatic hyperuricemia. This asymptomatic HU is a causal factor for many NCDs. Researchers now recommend that HU be included in the metabolic syndrome criteria.

A few diabetes patients may be asymptomatic; most hypertensive and dyslipidemia patients are asymptomatic. These patients are not referred to as asymptomatic diabetes, asymptomatic hypertension, or asymptomatic dyslipidemia but treated based on target values. Even painless acute myocardial infarction may come across. Pain should not be the criteria for diagnosis and treatment in metabolic disorders. Pre-hyperuricemia, like prediabetes and pre-HTN, needs to be screened, diagnosed early and managed to prevent the progression of many NCDs and their complications. Like prediabetes, pre-HU is also reversible with lifestyle modifications. HU and DM are siblings now; manage them with the same weapon. In the current century, hyperuricemia is diabetes equivalent. It should not be ignored that during the long journey of pre-HU to HU, the whole endothelium is exposed to inflammatory changes that may lead to the development of many NCDs and organ injuries. Prevention is always better than treatment and hence pre-HU deserves more attention to control the metabolic explosion.

Management of Pre-Hyperuricemia

Pharmacological: The available uric acid lowering drugs have more adverse effects and drug interactions. Present evidence does not satisfy to recommend pharmacological therapy in pre-HU. Treat other comorbidities with drugs that reduce UA, like losartan, fenofibrate, and SGLT 2 inhibitors.

Non-Pharmacological: The mouth is the gateway for many diseases, especially metabolic ones. Once the food entry is controlled, pre-HU and many metabolic disorders can be prevented. In pre-HU, lifestyle modification is cost-effective and straightforward. According to various studies, lifestyle measures reduce SUA by 1mg/dL [(63)]. Recommend a low purine diet, limit red meat, alcohol, and high fructose-containing food. Encourage low-fat milk products, adequate water intake, regular exercise, and maintaining ideal body weight. Maintain the SUA level at a safer level of less than 6mg/dL in men and less than 5mg/dL in women to prevent the development of systemic inflammation.

CONCLUSION

The epidemiology of hyperuricemia has changed globally during the last two decades due to the drastic change in our lifestyle, and its prevalence is on the rise. The uric acid controversies are melting now, and the association between hyperuricemia and non-communicable diseases is becoming clearer and stronger. The molecular mechanism involved is uric acid-induced systemic inflammation and endothelial dysfunction. This starts even before the present cutoff value of hyperuricemia which is proved by lowering the uric acid level; there is a reduction of inflammatory markers and even reversing many uric acid-related diseases. Uric acid could emerge as one of the most important risk factors ever identified for many NCDs in the near future. For getting acceptance, early diagnosis, treatment, and preventing the development of many uric acid-related diseases and their complications, the high normal value of serum uric acid may name as pre hyperuricemia. Lifestyle modification is the best measure we can adopt in this stage because of the non-availability of safe uric acid-lowering drugs. Identifying one step before the early stage of the disease is the best and intelligent method to prevent many cardio-reno-metabolic diseases. Maintain the SUA level at a safer level. The authors conclude this article with some exaggeration that if we can control SUA at the level below prehyperuricemia, we can `eradicate` this oldest disease gout, and prevent the development of many hyperuricemia-related diseases.

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