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A new concept to know about hypouricemia, when hyper makes all the noise!!

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Abstract
Aims and objectives: *To study clinical significance of hypouricemia and its associated conditions*
We present an approach to hypouricemia, which is defined as a serum urate concentration of < 2 mg/dL (119 µmol/L), for the consulting physician who first encounters the patient. Hypouricemia occurs mainly because of either decrease in urate production or promoting the elimination of urate via the kidneys.
Even though hypouricemia is not having clinical significance but it can be a sign of underlying disease Therefore, Physicians must recognize hypouricemia as a biomarker of various pathological and potentially harmful conditions, and refer the patient to required specialists for specific management.
Methods :*Literature search*
Conclusion :*Hypouricemia will provide us clues to underlying disease after finding etiology for hypouricemia. So physicians should be aware about the fact that hypouricemia per se is not having clinical significance but can be a sign of underlying pathological conditions.*
Key words :*Hypouricemia, Uric acid, Biomarker*

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I. Introduction

Urate metabolism gained much importance recently. Hypouricemia occurs due to a negative imbalance of urate metabolism.[1] Hypouricemia was first identified in 1950 and defined as a serum urate concentration of < 2 mg/dL (119 µmol/L).[2]Hypouricemia will provide a clue for underlying uncommon conditions.

It is reported mainly in Asian countries. Prevalence of hypouricemia in general population is 0.2 a 0.58% , and in hospitalized patients is 4.14% [3]Hypouricemia is more common among females compared to males.[4] Based on pathophysiologic mechanisms hypouricemia can classified into two main categories: (1) conditions associated with a decrease in urate production and (2) conditions promoting the elimination of urate via the kidneys (increased renal clearance).[5]

Methods : Literature search

Decreased production of urate

Inherited disorders of purine metabolism

Rare hereditary diseases that cause abnormalities in the synthesis and catabolism of purines are among the main causes of hypouricemia associated with a decrease of urate production.

Hereditary xanthinuria

Hereditary xanthinuria (HX) is an autosomal recessive condition produced by a deficiency of the xanthine dehydrogenase/oxidase enzyme. This is characterized by low urinary concentrations of urate and high urinary concentrations of xanthine, which lead to the development of urinary xanthine kidney stones.

Patients with a deficiency of the molybdenum cofactor have an increased risk of presenting thiopurine induced toxicity.[6]HX type 1 is associated with Mutations in the xanthine dehydrogenase (XDH) gene and it is distinguished by an isolated insufficiency of the enzyme xanthine dehydrogenase/oxidase, which catalyzes the conversion of hypoxanthine into xanthine and of xanthine into urate.

HX type 2 is caused by a mutation in the molybdenum cofactor sulfurase (MOCOS) gene. Clinically, insufficiency of the molybdenum cofactor is manifested by serious neurological diseases, dysmorphisms, and lens dislocation, which results in poor outcome.[7]

Table 1 Classification of Hypouricemia

Decreased production of urate
Inherited disorders of purine metabolism
Hereditary xanthinuria (HX)
Purine nucleoside phosphorylase (PNP) deficiency
Acquired conditions associated with decreased urate production
Urate-lowering drugs (xanthine oxidase inhibitors)
Urate oxidase (uricase derivatives)
Liver disease
Malnutrition
Increased urinary excretion of urate
Inherited disorders
Type 1 Hereditary renal hypouricemia
Type 2 Hereditary renal hypouricemia
Acquired disorders
Fanconi syndrome
Intracranial disease
Volume expansion
Drugs
Critically ill patients
Acquired immunodeficiency syndrome
Total parenteral nutrition
Diabetes mellitus

Purine nucleoside phosphorylase deficiency

Purine nucleoside phosphorylase (PNP) insufficiency is an autosomal recessive condition which occurs due to mutations in the PNP gene.Its prevalence is low and it is a rare condition. PNP metabolizes inosine into hypoxanthine and guanosine into guanine. Because of purine nucleoside phosphorylase deficiency there will be an inadequate conversion of inosine to hypoxanthine which further leads to functional deficiency of the hypoxanthine-guanine phosphoribosyltransferase enzyme.

PNP gene is located on the long arm of chromosome 14 and it can be diagnosed prenatally. Clinically manifests in the form of neurological abnormalities and severe combined immunodeficiency.[7]

Neurological involvement is characterized by spasticity, ataxia, developmental delay, mental retardation, and cerebrovascular disease. About 30% of these patients develop autoimmune disorders like systemic lupus erythematosus, idiopathic thrombocytopenic purpura and autoimmune hemolyticanemia. Assessment of PNP activity in lymphocytes or red cells in immune-deficient patients useful for diagnosis.[8]

Acquired disorders associated with decreased urate production

Among the acquired causes of hypouricemia associated with decreased urate production, the use of urate-lowering drugs (xanthine oxidase inhibitors such as allopurinol and febuxostat) and the use of uricase (an enzyme that converts urate into a) are noteworthy. Additionally, liver diseases and malnutrition (emaciation) correspond to this category.

Urate-lowering drugs (xanthine oxidoreductase inhibitors)

Febuxostat and allopurinol are commonly used xanthine oxidoreductase inhibitors for the treatment of hyperuricemia and gout. Benzbromarone is a noncompetitive inhibitor of xanthine oxidoreductase but is not approved by FDA due to concerns of acute liver injury. With these drugs the serum urate concentration usually does not fall below normal range.[9]

Urate oxidase (uricase)

Pegloticase is a pegylated,recombinanturicase enzyme used in the management of refractory chronic

gout. Pegloticase converts urate into allantoin (uricolytic action). The urease enzyme metabolizes the urate into the more soluble allantoin, which has 5–10-fold increased solubility compared to uric acid and it is easily excreted via the kidney.[9] Profound hypouricemia occurs with the usage of pegloticase, with urate levels of less than 2 mg/dL (119 μmol/L).[10] So consulting physicians should be aware that use of these potent drugs may result in over treatment of hyperuricemia leads to hypouricemia which further worsens acute gouty arthritis.

Liver disease

Hypouricemia occurs due to defect in the renal absorption secondary to loss of hepatic xanthine oxidase activity in severe hepatic obstruction.[5] Other liver diseases causing hypouricemia are primary biliary cirrhosis, Laennec's cirrhosis and hyperbilirubinemia.[11]

Malnutrition

Hypouricemia is associated with a higher risk of mortality among patients with low protein catabolic rate which suggest that it is a nutritional marker for predicting prognosis in patients under hemodialysis.[12]

Increased urinary excretion of urate

Inherited disorders

Renal hypouricemia (RHUC) is associated with low serum urate levels (≤ 2 mg/dL) due to molecular mechanisms like reabsorption insufficiency, defective tubular transport, and increased secretion of urate. RHUC is characterized by recessive mutations in genes encoding distinct urate transporters in the proximal renal tubule. Hereditary RHUC is divided into two types based on genetic mutations. Type 1 is due to mutations in the SLC22A12 gene, and type 2 is due to mutations in the SLC2A9 gene. Affected patients often remain asymptomatic, and some individuals develop nephrolithiasis and acute kidney injury, usually following exercise.[13]

Type 1 Hereditary renal hypouricemia

Hereditary RHUC1 is an infrequent autosomal recessive inherited renal membrane transport disorder affecting urate reabsorption in the proximal tubules, leading to hypouricemia and predisposing to urolithiasis and exercise induced acute renal failure.[13]

Type 2 Hereditary renal hypouricemia

GLUT 9 is the most important regulator of urate levels in humans. SLC2A9 gene encodes GLUT9, a transporter of urate from tubule cells. Mutations in the SLC2A9 gene results in e reduced urate reabsorption on both sides of the renal proximal tubules.[14]

Acquired disorders

Fanconi syndrome

Renal Fanconi syndrome occurs due to generalized dysfunction of the proximal tubule. There will be aminoaciduria, glycosuria, low-molecular-weight proteinuria and phosphaturia which leads to rickets. Hypouricemia in fanconi syndrome is due to altered reabsorption of urate. The Fanconi renal syndrome is associated with several inborn errors of metabolism or is acquired through exposure to certain drugs that induce mitochondrial dysfunction. Drug induced fanconi syndrome is due to outdated tetracycline antibiotics, chemotherapeutic agents, antiviral drugs, aminoglycosides, and anticonvulsant medications.[15]

Acquired disorders

Drugs

Routinely prescribed medications can decrease serum urate levels (blood pressure-lowering drugs, lipid-lowering medicines, medications used in the treatment of nutritional disorders, diabetes mellitus, obesity, hormones, drugs used to treat infections, some non-steroidal anti-inflammatory drugs (NSAID), and certain medicines prescribed for psychiatric and seizure disorders).

1. Uricosuric medications such as probenecid and benzbromarone inhibit transport of urate.[16]
2. Lesinurad is a selective oral URAT1 inhibitor which inhibits the transporter responsible for the majority of the reabsorption of filtered urate from the renal tubular lumen.[16]

3. The uricosuric action of the angiotensin II receptor blocker, losartan, an effective antihypertensive agent that has been used to treat hypertension.[17]

4. Fenofibrate inhibits URAT1 and produces hypouricemia due to an enhanced urinary excretion of urate.[18]

5. The most common drugs with uricosuric effect include high-dose trimethoprim-sulfamethoxazole and high-

dose salicylate therapy.[19]Aspirin causes hyperuricemia at low doses by reducing uric acid excretion and whereas higher doses it causes hypouricemia due to uricosuric effect. This paradoxical effect is mainly due to the interaction of salicylate with urate transporter URAT1.[20]

Critically ill patients

In patients with acute respiratory distress syndrome or sepsis there will be decreased reabsorption of urate due to release of proinflammatory cytokines.[21]

Acquired immunodeficiency syndrome

In acquired immunodeficiency syndrome (AIDS), an increase in urate excretion and hypouricemia has been reported as a result of defective urate management. Risk factors for hypouricemia in these patients are central nervous system infection, disseminated disease, and treatment with trimethoprim-sulfamethoxazole. Hypourecemia is prognostic indicator in AIDS patients.[22]

Total parenteral nutrition

There will be a decreased rate of urate production total parenteral nutrition and elemental enteral nutrition which results in transient hypouricemia. High glycine content of some parenteral nutrition formulations could be an associated factor.[23,24]

Diabetes mellitus

Glycosuria increases clearance of urate by increasing glomerular filtration rate. Long standing patients of diabetes mellitus may have hypouricemia due to glycosuria.[25]

Syndrome of inappropriate Antidiuretic secretion (SIADH)

Hypouricemia occurs in SIADH due to volume expansion and deficient post-secretory reabsorption. Water restriction improves hypouricemia. [26]

Hodgkin disease and other neoplastic conditions

Hypouricemia in hodgkin's disease occurs due to an isolated defect in the reabsorption of urate.[27] Solid tumors in children frequently have hypouricemia because of undernutrition and/or renal tubular damage attributable to treatment with antineoplastic agents.[28]

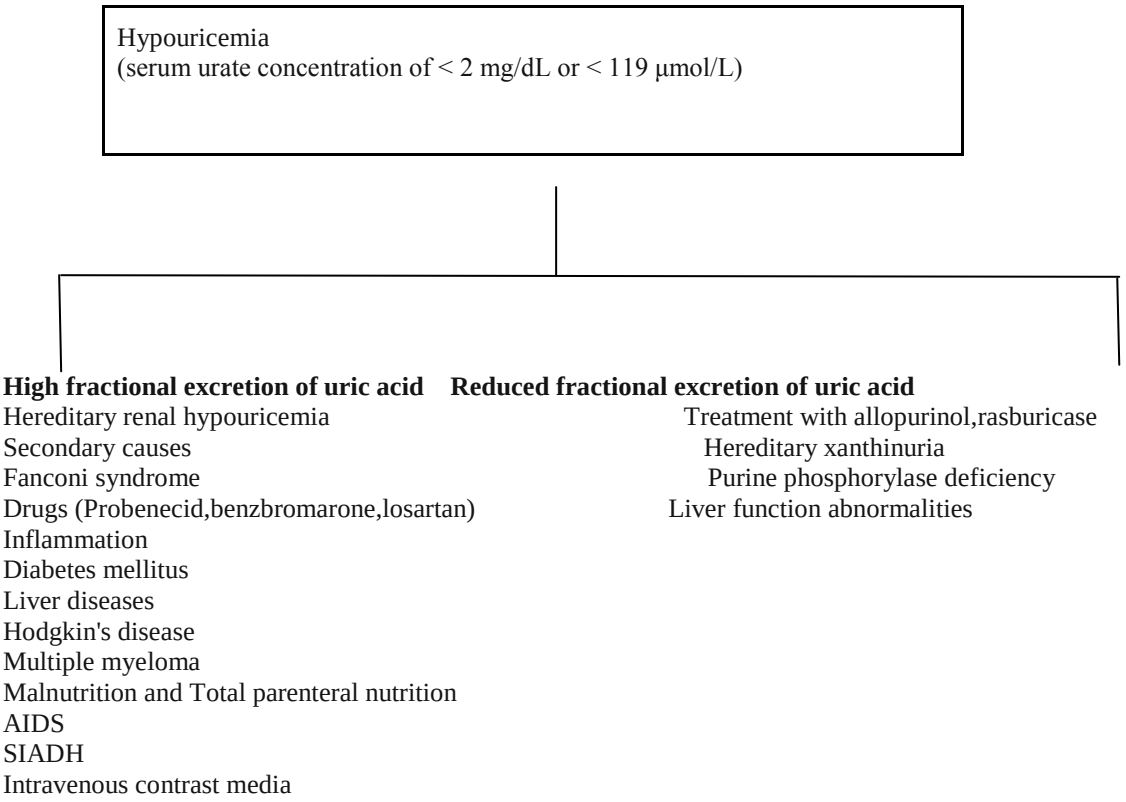

Fig 1. Algorithm for hypouricemia

(SIADH- Syndrome of inappropriate antidiuretic hormone secretion, AIDS- Acquired Immune Deficiency Syndrome)

Clinical significance of hypouricemia

From the beginning hypouricemia has been considered a biochemical abnormality and possesses low clinical significance. Even Though hypouricemia does not cause any specific signs or symptoms, hereditary RHUC has been linked to a higher prevalence of kidney disease and hypourecemia will serve as a prognostic factor among patients of chronic kidney disease on hemodialysis.[29,30]

Hypouricemia has a greater risk of deteriorating cognitive function and a higher prevalence of dementia and it is a risk factor for more rapid progression of the disease. It might be due to the antioxidant effect of uric acid and tissue-protective properties; thus, low levels are associated with an increased oxidative stress status.[31,32]

It's a well known fact that hyperuricemia is associated with higher cardiovascular mortality. Hypouricemia is also an important marker of malnutrition and is associated with cardiovascular risk and mortality.[33]
It has been observed that the reduction in the amount of serum urate (based on therapeutic guidelines when tophaceous gout is present) have raised concerns of safety of current serum urate targets (plasma urate target < 5 mg/dl), since a non-significant tendency was found toward higher mortality for those interventions leading to lower levels of serum urate.[33,34]

Diagnosis of hypouricemia

The diagnosis of hypouricemia is made when serum uric acid level < 119 μmol/L or 2.0 mg/dL. To make the diagnosis, it is suggested to confirm the serum levels of uric acid first. Once the diagnosis of hypouricemia is confirmed, it is important to find out the renal fraction of uric acid excretion, which will be increased (> 10%) in cases of increased excretion and decreased if hypouricemia is caused by conditions of underproduction.[35]

The exclusion of secondary causes of hyperuricosurichypouricemia (such as Fanconi syndrome, Wilson disease, and drug-induced tubulopathy) is important.

Congenital renal hypouricemia is diagnosed molecular analysis of the SCL22A12 and/or SLC2A9 genes.[36]

Treatment

There is no specific treatment for hypouricemia. Its management is based mainly on correcting the underlying cause and, in some cases, the patient may benefit from symptomatic treatment according to the clinical manifestations or complications that may occur during the disease.

In the case of exercise-induced acute renal failure when there is no intratubular precipitation of urate, it is thought that kidney injury is due to the increase in oxidative stress, as it is widely known that urate is a potent antioxidant. Therefore, treatment with vitamins C and E as antioxidants has been suggested. On the other hand, in cases in which there is a precipitation of urate crystals, management with xanthine oxidase inhibitors such as Allopurinol is recommended in order to reduce the concentration of urate, thus decreasing the likelihood of clogging these crystals.[37,38]

II. Discussion

This review focuses on the concept of hypouricemia and its physiopathological basis for the knowledge of the internal medicine physician who first encounters the patient.

The majority of articles included in this narrative review comprised epidemiological studies from Asian-population databases and from case reports of hereditary renal hypouricemia associated with mutations in the genes that encode tubular urate transporters.

Similar to gout, hypouricemia is caused by metabolic abnormalities in the production and excretion of urate, which can be further categorized in its primary and secondary forms. Hypouricemia is mainly caused by impaired renal transport of uric acid. It should be noted that primary forms include mutations in the metabolic pathways of purine degradation. Apart from hypouricemia these patients may have nephrolithiasis, immunodeficiencies, or diverse neurological manifestations. Therefore, hypouricemia, although a common finding, functions only as an ancillary biomarker in terms of its diagnosis.[39]

Among other causes, abnormalities in the production or increase of the oxidation of urate are the main causes that the rheumatologist will commonly encounter, including those caused by the use of drugs such as allopurinol, febuxostat, or pegloticase. In this manner, it will be important to take these into account in order to render an adequate diagnosis. However, the clinical impact and adverse outcomes of hypouricemia associated

with overtreatment with hypouricemic drugs in patients with gout has not, to our knowledge, been reported and remained as a research gap in the field.

Among the causes of hypouricemia due to increased urinary urate excretion, we find noteworthy the genetic causes, such as the different variants of hereditary renal hypouricemia and Fanconi syndrome, with the former abnormalities in the tubular transport of urate associated with recessive mutations in genes encoding distinct urate transporters in the proximal renal tubule.

This pathology exhibits a variable clinical presentation, ranging from asymptomatic subjects to patients with severe renal injury induced by exercise. In addition, this condition has recently been associated with severe neurological manifestations due to the increase in the production of free radicals that can take place urate levels ($\leq$ 2 mg/dL) in this condition.

In the diagnostic algorithm of hypouricemia, it is important to calculate the fractional excretion of urate (FEU) in order to differentiate the causes that are associated with a decrease in FEU, such as hypouricemia associated with xanthine oxidase inhibitors such as allopurinol or febuxostat. On the other hand, the causes associated with the increase in FEU include uricosuric drugs such as probenecid.

Patients with gout frequently have impaired glucose metabolism or established diabetes mellitus. It has been observed that patients with long-standing diabetes, especially those with insulin-dependent diabetes, may develop hypouricemia, probably caused by glycosuria.[25]

In addition, hypouricemia has been associated with a history of kidney disease, another common complication in patients with connective tissue diseases, such as systemic lupus erythematosus, and also, primary biliary cholangitis has been associated with hypouricemia due to abnormalities in the reabsorption of urate.

Treatment should be focused on treating the underlying cause and avoiding kidney injury or the formation of nephrolithiasis by maintaining patients adequately hydrated, administering antioxidants to them, and alkalizing the urine.

Hypouricemia can indicate wide spectrum disorders ranging from medication induced to neoplasias like hodgkin's lymphoma. Even during treatment of hyperuricemia, drug induced hypouricemia can precipitate the acute gouty arthritis, so physicians should be aware of this fact that low or normal serum uric acid is not an exclusion for gouty arthritis and close follow up is needed for patients with low serum uric acid .

III. Conclusions

The internal medicine physician should remember that hypouricemia is due to abnormalities in both the production and excretion of urate. Therefore, for its diagnosis, it is important to know the status of FEU and to initiate from this point the investigation of the underlying cause of the low-level urate serum concentration.

Likewise, it should be considered that hypouricemia is a fundamental biomarker that will allow us to reach an accurate diagnosis and that, depending on the etiology of the disease,its specific management can be carried out.

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