

Review

Gout, hyperuricemia and the metabolic syndrome

Guta, hiperuricemia și sindromul metabolic

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Abstract

Uric acid is a product of purine metabolism and hyperuricemia is considered to be the major etiological factor of gout. Actually, this metabolic arthritis is produced by the precipitation of monosodium urate monohydrate crystals within joints, triggering an inflammatory reaction. Hyperuricemia is often associated with metabolic syndrome and may lead to vascular endothelial dysfunction, thereby contributing to cardiovascular and renal diseases. Mechanisms associating metabolic syndrome and hyperuricemia imply an accelerated hepatic purine synthesis, related to hyperinsulinemia and enzyme induction. A high fructose intake was incriminated in the associated increased incidence of metabolic syndrome and hyperuricemia. Insulin stimulated enhanced reabsorption of urate from the glomerular filtrate may also contribute to hyperuricemia, increasing the relative risk of death. Evidence was also provided that physiological concentration of uric acid would exert antioxidant effects, attenuating neuronal lesions caused by oxygen radicals, generated during an acute ischemic stroke and in cases of neurodegenerative disorders.

Keywords: gout, uric acid, metabolic syndrome, cardiovascular disease, antioxidant effects.

Rezumat

Acidul uric este un produs de metabolism al purinelor, iar hiperuricemia constituie principalul factor etiologic în gută, această artrită fiind produsă prin precipitarea intraarticulară a cristalelor de urat monosodic monohidrat, care declanșează o reacție inflamatorie. Hiperuricemia se asociază frecvent cu sindromul metabolic și poate duce la disfuncții ale endotelilor vasculare, contribuind la patogeneza bolilor cardiovasculare și renale. Mecanismele prin care se asociază sindromul metabolic cu hiperuricemia implică o accelerare a sintezei hepatice de purine în legătură cu hiperinsulinemia și inducerea de enzime. Stimularea de către insulină a retroresorbției acidului uric din filtratul glomerular contribuie la hiperuricemie și la creșterea riscului relativ de deces. S-au adus și dovezi conform cărora concentrațiile fiziologice de acid uric ar exercita un efect antioxidant, atenuând leziunile neuronale cauzate de radicalii de oxigen produși în cursul unor accidente vasculare ischemice, precum și în cazuri de afecțiuni neurodegenerative.

Cuvinte cheie: gută, acid uric, sindrom metabolic, boli cardiovasculare, efecte antioxidante

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Table 1. Purine bases and their respective nucleosides and nucleotides

Base	Nucleoside (base + carbohydrate)*	Nucleotides (base + carbohydrate + phosphate)
Adenine (6 aminopurine)	Adenosine	Adenylic acid (AMP)
Guanine (2 amino 6 oxipurine)	Guanosine	Guanylic acid (GMP)
Hypoxanthine (6 oxipurine)	Inosine (hypoxanthine riboside)	Hypoxanthine ribotide
Xanthine (2 -6 dioxipurine)	Xanthine riboside	Xanthine ribotide

*The carbohydrate may be ribose or deoxiribose. According to Harper (8) slightly modified

The inflammatory arthritis caused by the deposition of monosodium urate monohydrate crystals into the joint cavity would result in gout, which was therefore considered to represent a metabolic joint disease. (1). Because acute gout attacks are painful, attention had been directed towards the pathogenic role of uric acid and evidence was provided that uric acid stones formation is responsible for renal colic.

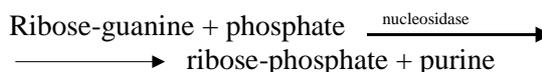
Gout and renal colic are not the only pathologic conditios associated with hyperuricemia, this metabolic disorder having been detected in obese, diabetic, hypertensive and hyperlipidemic patients, as well as in patients with renal failure (1-3).

More than 30 years ago, our laboratory investigated the behavior of uricemia in relation to the type of hyperlipoproteinemia and serum uric acid levels were found to be higher in subjects with type IIb and type IV, being also significantly correlated with serum triglyceride concentration (4). Because individuals with these types of hyperlipoproteinemia were compatible with the concept of metabolic syndrome and also displayed higher serum activities of liver-derived cholinesterase, gammaglutamyl-transferase and lecithin cholesterol acyltransferase (5, 6), it was considered that hyperinsulinemia and enhanced hepatic enzyme synthesis, presumably including those involved in purine metabolism may have contributed to both hypertriglyceridemia and hyperuricemia (4). Prevalence of metabolic syndrome in individuals with hyperuricemia was later reported by Choi and Ford (7).

A better understanding of mechanisms associating hyperuricemia to metabolic syn-

drome would require a presentation of the pathway of uric acid production and removal.

Uric acid is a product of purine metabolism and both adenosine monophosphate (AMP) and guanosine monophosphate (GMP) are submitted to the activities of deaminating enzymes and of nucleotidase which would split the phosphate bond. The resulting inosine and guanosine are subsequently converted to purine bases within a reaction catalyzed by nucleosidases (nucleoside phosphorylases) (8, 9).



Details on purine catabolism and uric acid formation are presented in *Table 1* and *Figure 1*.

It should be mentioned that, in opposition to most mammals, humans cannot oxidize uric acid to the more soluble allantoin, due to absence of uricase (uric acid oxidase). Presumably oxidase gene underwent functional mutation during the early stages of humanoid evolution (10).

The pool of purines undergoing catabolism may be provided by purine – rich food such as meat, especially viscera and fish, vegetables such as spinach and asparagus having a minor contribution. An accelerated turnover of nucleoproteines accompanying proliferative disorders of the hematopoetic system including leukemia, lymphoma, myelomatosis and polycytemia of any cause would lead to increased uricemia. Accelerated turnover of epithelial cells of the skin occurring in patients with psoriasis may result in moderately increased uric acid levels.

The most important source is however represented by endogenous hepatic synthesis of purine.

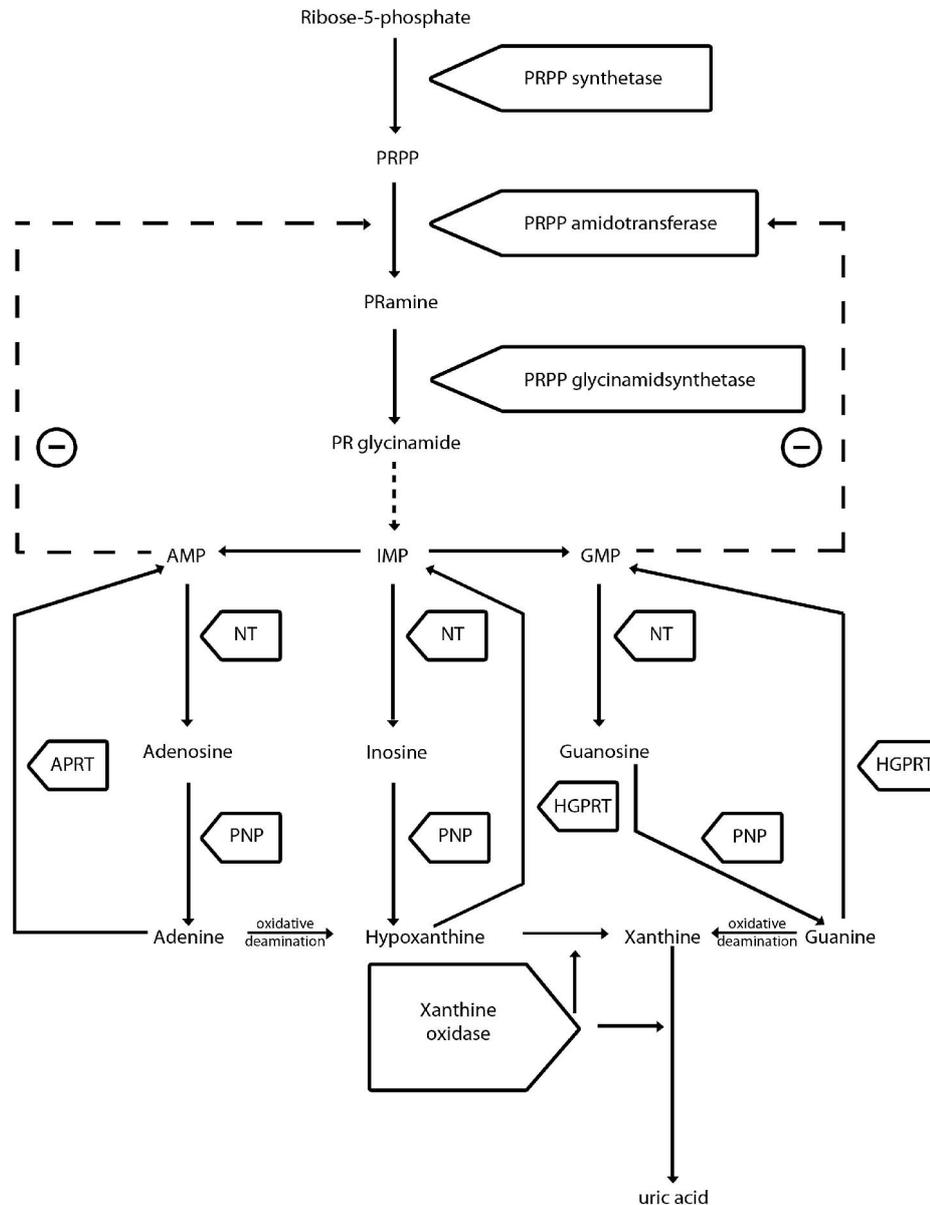
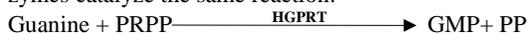


Figure 1. Regulated synthesis of purine nucleotides and the generation of uric acid

PRPP synthetase – phosphoribosylpyrophosphate synthetase; PRPP – phosphoribosylpyrophosphate; PR amine – phosphoribosylamine; PRPP glycinamide synthetase - phosphoribosylpyrophosphate glycinamide synthetase; PR glycinamide – phosphoribosylglycinamide; AMP – adenosine monophosphate; IMP – inosinemonophosphate; GMP – guanosinemonophosphate; NT – nucleotidase; PNP – purine nucleoside phosphorylase (nucleosidase); APRT-adenosine phosphoribosyltransferase; HG-PRT – hypoxanthine guanine phosphoribosyltransferase. According to data in the literature (1, 3, 8, 9, 11, 12). To be noted that in a recent publication the authors Jin et al 2012 (3) do not make distinction between HGPRT and APRT as these enzymes catalyze the same reaction:



Actually high serum uric acid levels were found in obese, diabetic, hyperlipidemic patients who were not afflicted by proliferative disease or by renal failure. Mechanisms involved in the control of hepatic purine synthesis should therefore be considered.

Synthesis of purine resulting in hyperuricemia

Evidence had been provided about a regulated synthesis of purines (*Figure 1*).

During an initial reaction ribose-5-phosphate acquires two phosphate molecules becoming a phosphorybosylpyrophosphate (PRPP). This reaction mediated by PRPP synthetase is potentiated by increased ribose-5-phosphate (the substrate) availability, this situation occurring in relation to an activation of the direct oxidative pathway of the carbohydrates (the pentoso-phosphate shunt). A diet rich in sugar (sucrose including glucose and fructose) would therefore increase the production of purines and subsequently the generation of uric acid (13-15). In a second sequence the amino group from the glutamine will be transferred to ribose-5-phosphate resulting PR-amine. The PRPP amidotransferase responsible for this reaction also plays a limiting role as its activity is inhibited by the generated nucleotides (AMP, GTP), but also by ATP and ADP (feed-back inhibition), thereby preventing an excessive accumulation of purines. The following steps imply an addition of glycine, a process mediated by PR glycinamid synthetase and the resulting glycinamideribonucleotide is submitted to formylation mediated by transformylases and the acquisition of another amino group also from the glutamine as well as the condensation with aspartate. The resulting nucleotides AMP and GMP are then involved in the control of various metabolic pathways.

As expected, disorders of enzymatic activities involved in purine synthesis would also influence the economy of uric acid. For example mutation in a gene located on X chromosome and controlling the synthesis of hypoxanthine guanine phosphoribosyltransferase (HGPRT) would severely impair the purine salvage pathway leading to a depletion of the nucleotides AMP and GMP known to inhibit PRPP amido-

transferase (*Figure 1*). The subsequent derepression of this enzyme involved in the early stages of purine synthesis would accelerate the synthesis of PR amine and PR glycinamide, yet such intermediate metabolites would not be salvaged thereby replenishing the nucleotide (AMP, GMP) pool, but would contribute to an excessive production of uric acid. Subjects afflicted by an HGPRT deficit, the Lesch Nyhan syndrome, would develop hyperuricemia resulting in gout and uric acid renal stone, while the purine deficit may be involved in neuropsychic disorders, including severe mental retardation, choreoathetosis, spasticity and self mutilation. To be noted that of all tissues, the brain is normally endowed with the highest HGPRT level and activity (16).

On the other hand, the „de novo” synthesis of purine occurs mainly in the liver which is particularly rich in PRPP amidotransferase, while other tissues such as bone marrow or brain are lacking this enzyme or display only very small activities. Purine synthesis in such extrahepatic tissues depends on the purine precursors provided by the liver, or by uptaking the purine released from degrading nucleotides.

It should also be remembered that the liver is irrigated by the portal flow rich in metabolites including fatty acids released from visceral adipose tissue, as well as hormones released from the pancreas, which may exert stimulating effects on the enzymes involved in purine synthesis. These anatomic and functional peculiarities may provide a pathogenic link of the metabolic syndrome and hyperuricemia. Noteworthy a prospective study is supporting this hypothesis, by demonstrating that individuals with higher serum uric acid levels, including young adults are at a higher future risk of type 2 diabetes (17).

Uric acid excretion

Because humans are not provided with uricase and are therefore unable to catabolize uric acid, the removal of any excess of this acid is ensured by its excretion.

About 25% to 33% of the generated uric acid is excreted by intestinal cells into the bowell

and eliminated. The most important and controlled excretion is however performed by the kidneys. Actually renal transport of urate was found to imply: a) glomerular filtration; b) near complete tubular reabsorption of the filtered urate; c) subsequent tubular secretion and d) partial postsecretory reabsorption in the proximal tubule (12). Evidence was also provided about a renal urate anion exchanger (URAT 1) which regulates blood urate levels (18). It was also found that many compounds may influence URAT-1 activity producing uricosuric or anti-uricosuric effects. It could be established that agents directly inhibiting URAT 1 from the apical side of tubular cells (such as probenecid, benzbromarone, sulfinpyrazone and losartan) are uricosuric. Conversely, antiuricosuric substances (for example nicotinate, lactate, β hydroxybutyrate, aceto-acetate) are used as exchanging anions within the tubular cells, being eliminated while urate is reabsorbed (12, 18). Noteworthy insulin was reported to increase reabsorption of uric acid, such a process occurring even in insulin resistant individuals (19, 20), thereby contributing to the hyperuricemia recorded in patients with the metabolic syndrome (4, 7). Besides insulin, angiotensin II (21) and parathyroid hormone (22) were also found to contribute to urate retention.

Interestingly, when compared to age-matched men, women display higher serum levels of leptin and significantly lower concentrations of serum uric acid, a finding suggesting a possible role of leptin in the regulation of uricemia (23). It should be remembered that leptin synthesis is greater in the subcutaneous adipose tissue (the gynoid fat patterning) than in the visceral one (the android type of fat deposition) (24). It was also demonstrated that estrogens stimulate leptin synthesis, which is inhibited by androgens (25).

The complex regulation of mechanisms involved in uric acid metabolism and excretion appear rather surprising for a waste product aimed at being discarded. Evidence was indeed provided that uric acid may exert not only deleterious but also beneficial effects, acting as both

proinflammatory yet also as an antioxidant. This balance is rather dangerously unstable, the above mentioned effects depending not only on uric acid level, but also on additional conditions.

The best documented noxious effect of hyperuricemia is gout (podagra)

Precipitation of monosodium urate monohydrate crystals may occur in any joint, but the first acute attack usually involves the big toe. Deposition of urate crystals also occurs in the synovial membrane and in connective tissue elsewhere, particularly Achilles tendon. Gouty arthritis is about ten times more common in men than in women (1). Deposition of urate crystals induces inflammation, the primarily responsive cells being the resident macrophages, which would release proinflammatory cytokines (TNF α , IL-1 β , IL-6, IL-8) leading to an influx of neutrophils (12, 26). A characteristic feature of acute gout is spontaneous resolution. This self-limited evolution involves several mechanisms, starting with the clearance of urate crystals from the joints, and continuing with an upregulation of IL-10 expression, apoptosis of inflammatory cells and proteolytic degradation of proinflammatory cytokines (12). Deleterious effects of hyperuricemia in cardiovascular and renal disease were attributed to an induction of endothelial dysfunction (27).

The above mentioned biochemic pathophysiological data are highly suggestive for an important pathogenic role of hyperuricemia and stimulated the initiation of prospective studies trying to assess whether this metabolic disorder may affect mortality (28) or whether hyperuricemia represents only another risk factor and should be considered as a target for treatment (29).

Usually hyperuricemia is defined as blood uric acid levels are above the normal reference range, namely greater than 7 mg/dl (416 μ mol/l) in men, and greater than 6 mg/dl (357 μ mol/l) in women. A more analytical separation of individuals into four quartiles according to the uric acid levels was found to be more pathogenically demonstrative. Uric acid values in the four quartiles were Q1: 0,3-4,9 mg/dl; Q2 5-6,4 mg/dl; Q3 6,5-8,4 mg/dl; Q4 8,5-13

mg/dl. When comparing to the relative risk (RR) of death in Q1 (RR= 1) the risk of death of all causes was slightly increased in Q3 (1,17; $p<0,05$), being significantly higher in Q4 (1,64; $p<0,01$). Interestingly RR for death in cancer was low in hyperuricemic patients (Q4: RR 0,60) and moderately increased in the hypouricemics (Q1: 1,28) owing to a presumably related antioxidant effect of soluble uric acid (30), a rather controversial item (31). Both low and high serum uric acid concentrations were found in patients with severe liver disease, depending on impaired hepatic purine synthesis or cholestasis and alcohol intake (28).

According to prospective studies on a large cohort, increased serum uric acid is a minor but significant risk factor for all causes mortality, but in most cases it is not an independent risk. Careful monitoring of uric acid level and of renal functions are justified in order to detect and delay the evolution towards end-stage renal failure (31, 32).

Uric acid as a survival advantage

As previously mentioned, the relatively higher uric acid level occurring in humans was considered to confer a survival advantage contributing to a longer life span. The increased serum uric acid level is due to distinct mutations in the uricase gene that made it nonfunctional. It was considered that uric acid might regulate blood pressure. Actually an experimental mild hyperuricemia could be induced by administering in rats the uricase inhibitor oxonic acid. These hyperuricemic rats placed on a low Na^+ diet maintained their blood pressure, while the control rats displayed a gradual fall in blood pressure when given the above mentioned low Na^+ diet. The increase in blood pressure was found to be partially mediated by a stimulation of the renin-angiotensin system which plays a key role in the regulation of blood pressure, glomerular filtration and sodium balance. The hominoids eating fruits and foliage thus being on a low sodium diet were advantaged by a mechanism which in such condition was able to elicit

an adequate cardiovascular response to a dangerous situation, thereby being life-saving. In a modern society on a high sodium diet this mechanism may have a role in the current epidemic cardiovascular disease (33).

Another beneficial effect attributed to uric acid is pertaining to its antioxidant qualities. It had been established that oxygen radicals exert toxic effects by initiating a chain of reactions leading to lipid peroxidation (rancidity) and the subsequent damage to DNA, RNA, cellular membranes and cellular organelles (34). An array of antioxidant protective mechanisms were fortunately developed including enzymes such as superoxide dismutase and glutathione peroxidase, lipophilic antioxidants and radical scavengers such as α tocopherol (vitamin E) and β carotene, as well as hydrophilic antioxidants including ascorbic acid (vitamin C), glutathione and uric acid. Evidence was provided that urate at physiologic concentrations is about as an effective scavenger of oxygen radicals as ascorbate. By preventing damage to DNA, it was considered that uric acid would exert anticarcinogenic and to extend life span (30, 35). An attenuation of neuronal damage had been noted in hyperuricemic patients with Parkinson's disease, Huntington's disease and also in those with multiple sclerosis (3). A moderately higher uric acid level was reported to increase the odds of good clinical outcome in patients with acute ischemic stroke (36), a finding reinforcing the relevance of oxidative damage in ischemic stroke.

It has been attempted to establish a connection between serum urate level and intelligence (1, 37), a statement rather difficult to evaluate, as individuals with HGPRT deficiency and subsequent Lesch Nyhan syndrome display extremely high uric acid levels and severe mental retardation (16). Impaired mental development in such children should rather be explained by severe purine depletion than by an increase of uricemia.

At the end one should mention that gout and hyperuricemia are too often forgotten, this metabolic disorder being underevaluated (38).

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