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Abnormal serum uric acid levels in health and disease: A double-edged sword

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Abstract: Abnormal serum uric acid (UA) level is a highly prevalent condition worldwide and is increasing in the general population. This alarming epidemiological trend has enormous public health implications due to the central role of abnormal serum UA levels in the initiation, progression, and long-term effects of many metabolic and systemic diseases. Metabolic disorders are major causes of global morbidity and mortality. Altered serum UA level, both above and below the reference ranges for individual traits and contexts, is potentially harmful and described by many researchers as a double-edged sword. Concrete prevention plans in susceptible individuals and treatments to restore normal levels in individuals already affected are advocated. Lifestyle adjustment, including regular moderate physical activity, weight management, healthy eating, and regular serum UA screening are recommended for individuals susceptible to derangement in serum UA levels due to age, sex, genetics, and other acquired conditions. Public health efforts to create awareness about the menace of abnormal serum UA levels, particularly in susceptible individuals, should be encouraged.

Keywords: Deranged Serum Uric Acid, Adverse Health Effect, Human

1. Introduction

Abnormal serum uric acid (UA) level is a major public health problem due to its pivotal role in the etiology of many systemic diseases. Epidemiological studies have identified serum UA level both below and above the reference range as a marker, independent risk factor, or both for metabolic and cardiovascular morbidity and mortality, a situation described as a double-edged sword [1].

Abnormal serum UA level is highly prevalent worldwide [2], and the number of people affected continues to rise [3]. This alarming epidemiological trend may herald a corresponding and imminent increase in associated complications, underscoring the need for urgent public health attention. Consequently, researchers have raised many questions about the mechanisms and causes of this derangement and its health consequences. Critics have partly blamed modernization for this trend, assuming that our ancestors may not have experienced many of the metabolic disorders present today. Our predecessors lived simple, less complicated lives, followed less risky lifestyle patterns, and ate simple yet nutritious diets and hence achieved longevity and were less prone to metabolic disorders. Most striking is the likelihood that our prehistoric ancestors had healthier serum UA levels, as was confirmed among the Yanomamo of southern Venezuela, who have average serum uric acid levels of 3 mg/dL [4] that may explain in part why they are less prone to diseases such as hypertension. The questions to be addressed include where have we gone wrong? Can we reverse the current trend? Can we conclude that the modern prevalence of abnormal serum UA levels in the general population is the central controlling factor in the etiology of disease conditions such as renal failure and cardiovascular, neurodegenerative, cerebrovascular, autoimmune, inflammatory, reproductive, musculoskeletal, endocrine, metastatic, and metabolic disorders? [1, 5-8]

This review addresses these questions.

2. Synthesis and Transport of UA, an Indispensible Molecule

UA is a weak acid (pka, 5.8) that is primarily found and distributed in the extracellular fluid compartment as monosodium urate, a final oxidation product of purine metabolism. When pH is <5.75, as may occur in urine, the predominant form is un-ionized uric acid [9], whereas at a pH

of 7.4, the ionized form circulates. When UA reaches concentrations above 6 mg/dL (oversaturation), it has a high propensity for crystallization and precipitation of monosodium urate in urine, body fluids, and soft tissues [10]. Conversely, purines are products of dietary and endogenous nucleic acid metabolism, a pathway catalyzed by a number of enzymes. Specifically, UA is produced from xanthine via the action of xanthine oxidase, an enzyme that converts hypoxanthine to xanthine. Additionally, the activities of guanine deaminase, which converts guanine to xanthine, can also promote UA production. UA can be synthesized directly from 5-phosphoribosyl pyrophosphate and glutamine (Fig. 1) [11]. In the absence of uricase in humans, a more soluble compound, allantoin, is not produced, hence limiting the pathway to urate production and excretion in urine [11]. The amount of UA within physiologic fluid (synovial fluid/blood plasma), especially blood plasma, depends on three pivotal control points—namely, dietary purine intake, urate biosynthesis (uricolysis), and rate of urate excretion. Most of the UA generated daily is excreted from the kidneys (approximately 70%) and the rest from extra-renal routes including the intestines, skin, hair, and nails [12, 13]. UA is produced in the liver and intestinal mucosa [13] as well as in the microvascular endothelium at various sites such the mouth, airway, heart, and brain [14-16].

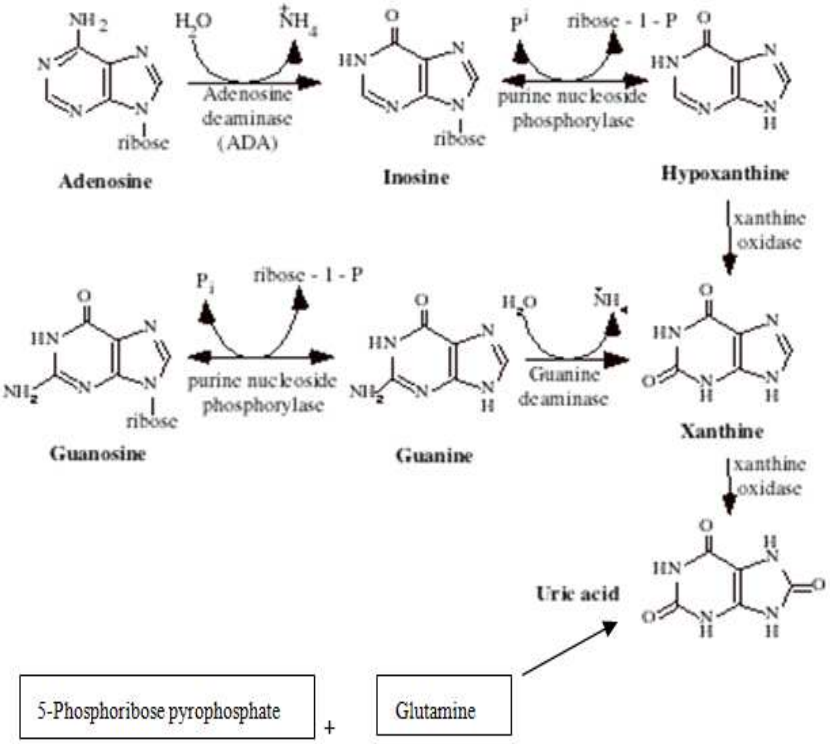

Figure 1. *Pathway for uric acid synthesis*

Various physiological mechanisms reportedly occur in the kidneys for tight control of plasma urate clearance via glomerular filtration, reabsorption, secretion, and post-secretory absorption [17]. However, some authors contest this aforementioned four-mechanism model and suggest a continuous and simultaneous reabsorption-secretion phenomenon along the tubular compartments [18].

In the kidney, approximately 90–95% of UA filtered at the glomeruli is reabsorbed from the proximal renal tubule, whereas active secretion into the distal tubule takes place through an ATPase-dependent mechanism [19]. A number of urate transporters, including human urate transporter (hURAT) 1 and hURAT2, are responsible for urate reabsorption, whereas organic anion transporters (OATs) such as OAT_1 and OAT_3 and the ATP-dependent urate export transporter- MRP_4 (multiple drug resistant protein-4) are involved in urate secretion [20,21]. URAT1 is located on the apical tubular membrane. UA has low solubility in water and plasma, and persistent high serum UA levels predispose individuals to urate crystal deposition within soft tissues, an integral factor in the pathogenesis of gout [22].

To establish urate balance, the body manages the rates of urate production and excretion; therefore, any derangement in urate homeostasis results in abnormal serum UA level (hyperuricemia or hypouricemia), a condition that can be considered a double-edged sword in terms of its effects on the body in health and disease.

3. "Normal" Serum UA Level

Normal serum UA acid level is still being debated. In many countries, 7 mg/dL for men and 6 mg/dL for women are accepted as the upper limits of normal, and approximately 2 mg/dL for men and women is the lower limit. However, these values have been adopted for individuals without clinical evidence of gout [10]. Some authors have proposed that a

threshold of <6.0 mg/dL should be adopted as the normal reference value for UA based not on the distribution of its circulating levels in the general population but on its physiological role and pathophysiological involvement in human disease[10]. In some individuals, levels slightly above this upper limit might be considered normal. The view is that serum UA concentration should be a range, but not fixed, and hence could vary from person to person. In other words, what is considered normal in one patient could be considered abnormal in another based on the outcome and not on the value. For example, Obermayr et al [23] stratified study subjects into three groups: those with normal UA levels (<7.0 mg/dL), modestly elevated UA levels (7.0–8.9 mg/dL), and markedly elevated UA levels (≥9. 0 mg/dL).

Therefore, under physiological conditions and with minimal exposure to confounding factors, serum UA levels between 2 and 7.0 mg/dL in males and between 2 and 6.5 mg/dL in females could be considered normal [23-27]. Serum UA levels persistently below 2 mg/dL (hypouricemia) and above 7 mg/dL (hyperuricemia) for individual traits and contexts are considered abnormal and may predispose patients to metabolic deficits and disease complications. Another interesting fact is that serum UA levels vary across the menstrual cycle in most healthy premenopausal women, and in addition to estrogen, rising levels of progesterone can also induce uricosuric effects in women [28]. Hence, menstrual cycle should be considered when measuring serum UA in women.

Certain modifiable (e.g., lifestyle, physical activity, and diet) and unmodifiable (genetic/inherited or idiopathic) factors can shift UA levels from normal to abnormal. Many experts consider abnormal serum UA level to be the underlying cause of certain diseases, whereas others believe that it is only a consequence, indicator, or even predictor of underlying disease conditions. Yet others view it as an active participant, not an innocent bystander, in many disease entities. Still others see it as "a friend and a foe." Hence, abnormal serum uric levels might operate on a two dimensional effect principle in many disease conditions [6, 21, 24, 27].

Consequently, although abnormal serum UA levels have been regarded in recent studies as independent predictors of renal dysfunction in rheumatoid arthritis and congestive heart failure [29, 30] and as risk factors that precipitate complications in renal failure and many cardiovascular, neurodegenerative, cerebrovascular, autoimmune, inflammatory, and metabolic diseases [5-8], another school of thought is that these derangements could have some advantages—as measures of protection against long-term complications in some diseases and as targets for treatments in many neurological diseases. In effect, UA may have a positive effect in certain diseases [31-33]. For example, in the management of gout, lowering serum UA level has proved a potent treatment target, whereas raising serum UA has been beneficial in multiple sclerosis (MS) [34,36]. Although it is uncertain whether MS and Parkinson's disease (PD) patients have gout, a handful (although a negligible percentage) have presented with both conditions. In such presentations, much doubt exists about whether increased serum UA levels in gout could protect against MS/PD or vice versa; however these subjects may have other predisposing confounding factors such as lifestyle patterns, high physical activity levels, infections, asymptomatic metabolic deficits, or diet/herbal medication or alcohol use. The possibility of "risk reversal" exists in subjects with complications of low UA that have been protected from the complications of high UA; however, this hypothesis requires further research. In some studies, altered serum UA level is an independent predictor of mortality in many end-stage diseases in the presence of other comorbid conditions [36-38], and in others, altered serum UA levels might slow the long-term effects of these underlying diseases [34,39].

3.1. UA Homeostasis in Health and Diseases

In healthy subjects, the body tightly regulates the production, utilization, and excretion of UA by controlling cell turnover of purine intermediates, filtration, reabsorption, and secretion. Physiologically, plasma UA concentration may be influenced by age, gender, race, and even physical activity [40-43]. It can also vary by as much as 50–120 μmol/l during the day in the same individual due to the effects of diet and exercise [44]. Normally, its excretion depends on plasma levels of urate. The upper limits of normal daily urinary urate excretion are 750 mg for women and 800 mg for men, whereas the lower limit is 250 mg [45-47]. However, excretion varies with body weight and size. Fractional excretion of UA (FE-UA) is estimated to range from 4% to 14% (6–12% in men and 6–20% in women) [48, 49].

Newborns have UA levels between 2.0 and 6.2 mg/dL, whereas levels in children range from 2.5 to 5.5 mg/dL [46]. Boys aged 10–18 years have levels of 3.6–5.5 mg/dL, and in girls in this age range, levels fall between 3.6 and 4.0 mg/dL. Compared with girls, boys experience a greater rise during puberty. Adult men (>18 to <40 years) normally have UA levels between 2 and 7.5 mg/dL, whereas adult women in the same age range have levels between 2 and 6.5 mg/dL. In men aged >40 years, levels range from 2 to 8.5 mg/dL, and in women aged >40 years, levels fall between 2 and 8.0 mg/dL. However, due to the uricosuric effects of estrogen (in consonance with progesterone), which is abolished during menopause, values rise steadily in menopausal women compared with those of non-menopausal women [28, 40, 50,51]. Because aging can contribute to low muscle mass, it may also cause a rise in serum UA, supporting the theory that elevated UA may lead to sarcopenia [52].

The intensity and duration of physical activity can also influence serum UA levels. Sutton et al [53] found that plasma UA concentrations in 15 men increased from 6.9 to 8.5 mg/dL after a 5000-m race and from 6.2 to 7.9 mg/dL in 11 men after a marathon (42 km). During a progressive exercise test on a cycle ergometer, the plasma concentration did not change significantly in these 11 subjects. However, plasma oxypurine levels and the urinary excretion of oxypurines increased, and intracellular ATP decreased while adenosine monophosphate (AMP) and adenosine diphosphate increased.

In a parallel study by Green and Fraser [54], the effects of exercise intensity and short-term training on alterations in

plasma UA level were investigated in two series of subjects aged 19–25 years. The first group of subjects cycled at 120% maximal oxygen consumption for 1 min followed by 4 min of recovery until fatigue or until 24 repetitions had been completed; the second cycled continuously at maximal oxygen consumption for 2 h. The results showed a significant post-exercise increase in UA, suggesting that exercise intensity rather than work output is the critical factor mediating increases in blood UA concentration. The results further reaffirmed that UA formation can arise from purine nucleotide degradation and fast-twitch fiber utilization during conditions of high energy utilization. Although exercise can be considered a health management therapy in many cardio-metabolic diseases, some empirical studies have shown an association between intense physical activities; profuse sweating in hot climates, reduced urinary acid excretion, and hyperuricemia[54-56]. Similarly, acute renal failure after exercise at various rates has been reported in studies among patients with familial renal hypouricemia (RHUC) [47,57,58] and may be attributable to exercise-induced oxidative stress among other factors. Because familial RHUC is mostly asymptomatic, serum UA screening should be conducted in affected individuals before any physical training [57] to identify potential risks.

Some studies have tried to establish racial/ethnic background as a socio-demographic factor in susceptibility to the development of abnormal serum UA levels and metabolic syndrome. Studies have been conducted among Hispanics, whites, African-Americans, Asians, and Arabs [59-62], and the results showed, for example, that African-American descent is associated with a greater than 50% increased risk for gout in both men and women compared with that in whites [61]. De Boer et al [62] found that in a group of non-Hispanic white, non-Hispanic black, and Hispanic adolescents aged 12–19 years, non-Hispanic white males and females had the highest UA levels. Conversely, the prevalence of RHUC is reportedly more frequently in Asian and Arab populations than in populations of other races [47]. These findings are inadequate for drawing inferences because further studies must be performed in additional populations. Increased serum UA or the prevalence of hyperuricemia appears to be associated with the lifestyle choices and economic growth and development resulting from urbanization and westernization [44, 63-65].

Many other factors that regulate UA homeostasis can influence the balance of UA production with the excretion of urate by the kidney and are endogenous or exogenous, genetic, or environmental. Any derangement in this homeostasis is described as either hypouricemia or hyperuricemia.

3.2. Hypouricemia

Hypouricemia is arbitrarily defined as a serum urate concentration of <2 mg/dL. This condition occurs in approximately 2% of hospitalized patients and <0.5% of the non-hospitalized population [66]. Hypouricemia can be a consequence or cause of various physiological or pathological conditions in which there exists an underproduction of urate or increased excretion of urate in opposition to hyperuricemia. It can also result from decreased UA oxidation due to treatment with uricase and decreased renal tubular reabsorption due to inherited or acquired disorders. The possibility that abnormalities in intestinal uricolysis will produce hypouricemia is still under investigation.

Unmistakably, hypouricemia is not a disease condition itself (it is benign) and has been considered a biochemical disorder with no clinical significance other than as a marker of underlying disease [67, 68]. It is a medical sign that presents due to confounding factors that can be dietary or related to drugs/treatment procedures, genetics, or even physical activity and is often due to an underlying medical condition (Table 1). When analyzed, these factors might give a clear picture of the underlying etiology of hypouricemia. [67, 69, 70].

For example, the coexistence of hypouricemia and hyponatremia often differentiates the syndrome of inadequate secretion of antidiuretic hormone from most causes of hyponatremia [71], whereas hypouricemia and hypouricosuria are considered manifestations of renal tubular damage in primary biliary cirrhosis [72], hypouricemia in the syndrome of inadequate secretion of antidiuretic hormone is primarily the consequence of high UA clearance related to a decrease in tubular UA reabsorption [73].

Chronic consumption of certain foods is associated with serum hypouricemic effects. These foods are categorized as low-purine foods and include kidney and lima beans, coffee, whole-grain bread, asparagus, cauliflower, mushrooms, peas, cereals, and poultry such as chicken, duck, and turkey (see Table 1) [21,74,75].

Additionally, a common long-term effect of mostly vegetarian diets is hypouricemia due to the low purine content of consumed foods [76]. Szeto et al [77] assessed the effects of long-term vegetarian diets and found that they result in mean serum UA value as low as 2.39mg/dL Although consuming a vegetarian diet may be very beneficial for hyperuricemic and gout patients, a note of caution is warranted to prevent associated health conditions that may ensue.

Transient hypouricemia can also be a result of total parenteral nutrition (TPN), a health care intervention for patients immobilized by a serious disease condition. Strangely enough, TPN may produce hypouricemia followed shortly by acute gout, a condition normally associated with hyperuricemia[78-80]. The underlying mechanisms for this phenomenon remain unclear and understudied but may include prolonged starvation, interference from other chemical components of TPN, or decreases in UA related to the administration of uricosuric medications [78-80]. Various studies have reported that mutations in proteins responsible for the excretion of urate by the kidneys can lead to defective renal urate handling. Implicated genes include *SLC2A9* (solute carrier family 2 [facilitated glucose transporter] member 9), *ABCG2* (ATP-binding cassette, sub-family G member 2), *SLC17A1* (solute carrier family 17 [organic anion transporter] member 1), *SLC22A12* (solute carrier family 22 [organic anion/urate transporter] member 12), *GCKR* (glucokinase regulatory protein), and *SLC16A9* (solute

carrier family 16 member 9), also known as monocarboxylate transporter 9. For example, *SLC22A12* encodes for URAT1, whereas *SLC2A9* encodes for GLUT9, a member of a family of hexose (fructose and glucose) transport-facilitating proteins. The isoform GLUT9L is expressed on the basolateral membrane of proximal tubules, and the GLUT9S isoform is expressed on the apical membrane of the proximal tubules. Mutation in *SLC2A9* can result in defects in the activities of GLUT9, which depends on *SLC2A9* for regulation. Two kinds of genetic disorders cause hypouricemia: mutations causing xanthine oxidase (XO) deficiency, which reduces UA production, and mutations causing abnormal kidney function, which increases the excretion of UA (reduction in urate reabsorption), collectively known as familial RUHC types 1 and 2 (an autosomal recessive trait). In humans, loss-of-function mutation in *URAT1* is reportedly associated with presecretory reabsorption defects and hence the underlying etiology of RHUC type 1 [25, 81, 82, 83]. Conversely, RHUC type 2 is characterized by a reduction in urate reabsorption on both sides of tubular cells and an FE-UA rate higher than 150% [47]. It is worth emphasizing that hypouricemia with reduced FE-UA is associated with defective UA production, whereas hypouricemia with increased FE-UA is associated with defective proximal tubular transport of UA [84].

Renal hypouricemia can be classified into four [25] or five [83] types based on response to the pharmacological inhibitor pyrazinamide: (1) defective presecretory reabsorption, (2) defective postsecretory reabsorption, (3) enhanced urate secretion, (4) subtotal defect in urate transport, and (5) total inhibition of urate reabsorption. Four mutations in *hURAT1* in subjects with presecretory reabsorption defects (which impair the urate-transporting activity of hURAT1)—G774A, A1155T, and 1639-1643 del-GTCCT—were previously reported [81, 85, 86], and T1253G is a newly identified defect. As reported in one patient with idiopathic RHUC whose FE-UA was 95% compared with 10% in normal individuals, a homozygous G774A mutation of *SLC22A12* resulted in the formation of truncated and inactive hUART1. Because the A1145T and T1253G mutations were located in the ninth and tenth putative transmembrane domains, these mutations might modulate urate permeability via hUART1 [87]. However, a study by Wakida et al [83] showed that *hUART1* might be the gene responsible for presecretory reabsorption defects in RHUC, and a different gene might control post-secretory reabsorption defects owing to an absence of discernible *hUART1* mutations in subjects with postsecretory reabsorption defects.

Other inborn errors that may decrease UA production are hereditary xanthinuria (a recessive trait) and pure nucleoside phosphorylase deficiency. Mutation of the xanthine dehydrogenase (XDH) gene (located on chromosome 2p22-23) is the underlying cause of xanthinuria, which is either type I or II. Type I results from isolated XDH deficiency, whereas type II results from a dual deficiency in XDH and aldehyde oxidase [88, 89]. Aside from inborn errors, acquired disorders can also cause defects in UA metabolism.

Complications of RHUC include exercise-induced acute renal failure (EIARF) and urolithiasis, hematuria and nephrolithiasis related to UA, calcium oxalate, or both, in addition to aciduria and hyperoxipurinemia [47, 58]. Other disease conditions associated with hypouricemia [21, 60, 73, 90-93] are presented in Table 1.

Table 1. *Etiology of hypouricemia and some associated diseases*

Urate underproduction
➢ Primary (idiopathic) hypouricemia
➢ Secondary hypouricemia
• Excessive consumption of low-purine foods[a]
• Vegetarian diet
• Total parenteral nutrition
• Partial-complete xanthine oxidase inhibition/deficiencies
• Drugs (e.g., xanthine oxidase inhibitors)
• Folic acid deficiency anemia /molybdenum cofactor deficiency
• Zinc deficiencies
• Hereditary xanthinuria
• High copper/iron disorders—e.g., porphyria and hemochromatosis
• Cirrhotic liver failure
• Pure nucleoside phosphorylase deficiency
Urate overexcretion
➢ Primary renal hypouricemia
• Familial renal hypouricemia (types 1 and 2).
➢ Secondary hypouricemia
➢ Renal tubular dysfunction.
• Acute tubular necrosis
• Type 2 proximal tubular acidosis
• Interstitial nephropathy
• Fanconi disease
• Drugs/drug toxicity: uricosurics and diuretics
• Probenecid
➢ Other mechanisms
• Pregnancy (third trimester); preeclampsia and toxemia of pregnancy
• Tissue hyperperfusion/volume expansion
• Syndrome of inappropriate antidiuretic hormone
Diseases associated with hypouricemia
• Wilson disease
• Alzheimer's disease
• Multiple myeloma
• Nephritis/nephrolithiasis
• Cancer
• Parkinson's disease
• Type 1 diabetes mellitus
• Exercise induced acute renal failure
• Reversible posterior leukoencephalopathy syndrome

[a] Low-purine foods include whole-grain breads/butter, kidney and lima beans, vinegar, cereals, coffee, cheese, chocolate, cauliflower, poultry (chicken, duck, and turkey), rice, olives, eggs, milk, fruits (especially cherries). Moderate-purine foods include asparagus, spinach, fish, meat, mushrooms, lentils, and shellfish.

3.3. Hyperuricemia

Defined as a blood UA level of >6 mg/dL in women and 7.0 mg/dL in men [23], hyperuricemia can result from overproduction or decreased excretion of UA or a mixture of both. Hyperuricemia can be transient or asymptomatic; however, chronic hyperuricemia has been implicated in the pathogenesis of many diseases, including cardiovascular disease [94, 95], cancers [24], renal disease [96, 97], type 2 diabetes mellitus [98], and chronic nonspecific musculoskeletal pain [99].

Many factors, both modifiable and unmodifiable have been

implicated in the etiology of hyperuricemia, and they can be dietary, genetic, or acquired. As discussed previously, UA is a product of purine metabolism, and therefore, excessive and prolonged consumption of high-purine foods is associated with increased serum UA levels [100-102]. However, a purine-rich diet is a common but minor cause of hyperuricemia, because if the renal UA handling system is efficient, UA accumulation will not raise concerns. Moreover, considering the variation in the purine content of foods, diet alone is insufficient to cause hyperuricemia but instead can exacerbate its complications [100].

The sweetening industry has begun using additives such as high-fructose corn syrup, table sugar, and honey, all of which are rich in fructose. Today, most sweetened processed foods such as pastries are laden with high-fructose corn syrup [103]. Fructose has high purine content and when consumed in significant amounts in western diets, it is implicated in the pathogenesis of metabolic syndrome [104] and hyperuricemia. [105]. Unlike other sugars, fructose causes a rapid rise in serum UA levels. In fact, daily consumption of more than four brands of fructose-sweetened soft drinks imparted an odds ratio of 1.82 for hyperuricemia in a US population [106].

Increased fructose intake has been hypothesized to raise serum UA levels by increasing ATP degradation to AMP and activating the pathway of purine degradation to urate [107,108], a cascade of processes that begins with fructose phosphorylation [109]. Other mechanisms may also include the production of reactive oxygen species, activation of cellular stress pathways, and increase in UA synthesis [110]. Furthermore, fructose reportedly inhibits UA excretion, apparently by competing with the access of UA to the transport protein SLC2A9 [111]. Aside from fructose, substrates such as sorbitol, sucrose, lactate, and methylxanthines [112] increase serum urate concentration.

It remains rather controversial whether high-fructose sweeteners cause hyperuricemia or increase the risk and complications of hyperuricemia. Intervention studies such as those of Johnson et al [113], MacDonald [114], Emerson [115], and Fox [116] found that the consumption of fructose experimentally induces an acute rise in serum UA concentration. Conversely, Crapo [117], Huttenen [118], Curari [119], Osei [120], Anderson [121], Koh et al [122], and Grigoresco et al [123] observed no influence of fructose on serum UA concentration.

Most intriguing, Sun et al [124] found that increased dietary fructose intake was not associated with increased risk of hyperuricemia, whereas increased dietary alcohol intake was significantly associated with an increased risk, and increased fiber intake was significantly associated with decreased risk. These findings are consistent with those of other intervention studies that found associations between alcohol consumption and increased serum UA levels [101, 125].

Beer, spirits, wine, and liqueur influence UA concentration. In fact, beer intake is an independent factor for serum UA increase [126] due both to its alcohol content and its high-quality purines [127]. Beer intake increases UA more effectively than liqueur, but moderate wine intake does not increase UA [102,127]. As a by-product of fermentation, beer has a high purine content that is predominately present as readily absorbable guanosine, and its intake enhance urate production, compounding the stimulatory effect of alcohol metabolites on renal urate reabsorption [128]. Ethanol increase urate synthesis by enhancing the turnover of adenine nucleotides [129]. Acutely, excess consumption of alcohol may cause temporary lactic acidemia (lactic acidosis), reduced renal urate excretion, and induced hyperuricemia. Chronic alcohol intake stimulates purine production by accelerating the degradation of ATP to AMP via the conversion of acetate to acetyl-coenzyme A in the metabolism of alcohol [130]. Hence, alcohol intake increases UA concentration by reducing excretion [131,132] and increasing urate production [129]. Additionally, ethanol decreases the excretion of UA by promoting dehydration and (rarely) clinical ketoacidosis [128].

Table 2. *Etiology of hyperuricemia and some associated diseases*

Urate overproduction
- Primary hyperuricemia: Enzymatic defects leading defective purines degradation
  - Hypoxanthine-guanine phosphoribosyl transferase deficiency (partially in Seegmiller syndrome and completely in Lesch–Nyhan syndrome)
  - Phosphoribosyl pyrophosphate synthetase super activity
- Secondary hyperuricemia
  - Excessive consumption of high-purine diet foods[a]
  - Ketogenic diet
  - Diseases of purine degradation: high nucleotide turnover
  - Rapid cell proliferation or death: blast crisis of leukemia, psoriasis, lymphoproliferative diseases, rhabdomyolysis, and cytotoxic/chemotherapy.
  - Increased ATP breakdown: vigorous muscles exertion; glycogen storage diseases types iii (amylo-1,6-glucosidase deficiency), iv (glycogen branching enzyme 1 gene mutation), and vii (liver glycogen phosphorylase deficiency) can result in hyperuricemia from excessive skeletal muscle ATP degradation.

Urate underexcretion
- Primary (idiopathic) hyperuricemia
- Secondary hyperuricemia
  - Renal insufficiency leading to decreased glomerular filtration rate
  - Decreased tubular secretion (diabetic ketoacidosis, lactic acidosis)
  - Enhanced tubular reabsorption: in diuretic therapy and in diabetes insipidus
  - Others: lead nephropathy, hypertension, drugs (low-dose salicylate, ethambutol, and others)
  - Mixed (overproduction and underexcretion).
- Glycogenosis type 1 (glucose-6-phosphatase deficiency) and aldolase B deficiency
- Starvation: starvation ketosis
- Tissue hypoperfusion `
- High alcohol consumption: results in accelerated hepatic ATP breakdown and organic acid generation that competes with urate for tubular secretion
- High fructose consumption
- Environmental stressors/infections
- Socioeconomic confounding factors/lifestyle attitudes predisposing individuals to metabolic syndrome X and obesity

Diseases associated with hyperuricemia
- Gout
- Urolithiasis
- Acute uric acid nephropathy
- Cardiovascular diseases—e.g., hypertension, preeclampsia, stroke
- Cancer
- Type 2 diabetes mellitus and other insulin resistance syndromes

[a] High-purine foods include anchovies, consommé, legumes, meat extracts, organ meats (kidneys, liver, and brains), roe (fish eggs), sardines, tofu, mincemeat, and yeast.

The consumption of foods with diuretic properties has been associated with the incidence of mild asymptomatic hyperuricemia. These foods (mostly herbs and fruit juice) have inhibitory effects on renal UA excretion and include eggplant, garlic, cucumbers, cranberry, lemon, and asparagus, among others [133].

Starvation and fasting, which are modifiable factors, have been associated with the etiology of hyperuricemia, presumably due to the effect of ketones on UA excretion. This phenomenon can be observed among prolonged fasters, particularly during Ramadan [11,134]. Other modifiable and un-modifiable factors associated with hyperuricemia are presented in Table 2.

4. Serum UA as an Antioxidant and Pro-Oxidant

In humans, more than half of the antioxidant capacity of the plasma comes from serum UA. More specifically, UA represents approximately 60% of the total human serum antioxidant status [135]. As a direct-acting, low-molecular-weight antioxidant, UA controls the rate and activities of free radicals, especially reactive oxygen and nitrogen species (singlet oxygen, peroxyl, and hydroxyl radicals) whose activities that predispose cells and tissues to oxidative stress and damage. Under certain conditions, UA in the cell milieu also gives off an electron as an antioxidant to become a urate radical that can be regenerated to UA by ascorbate. Conversely, as a strong reducing agent similar to ascorbic acid, UA (urate radical) can act as a pro-oxidant under many conditions (especially during periods of lower ascorbate availability). Hence, as a pro-oxidant, UA causes disease, but as an important antioxidant, ameliorates disease conditions [136,137]. Thus UA can act as a friend or a foe depending on the preexisting cellular environment and its oxidative state.

During purine metabolism, the activities of the enzymes xanthine oxidase and xanthine dehydrogenase produce UA, superoxide, and reduced nicotinamide adenine dinucleotide [138]. Superoxides in turn react with nitric oxide to form peroxynitrite, an oxidant. However, UA in turn scavenges peroxynitrite, preventing peroxynitrite-induced tyrosine nitration [139]. Conversely, superoxide peroxidase catalyzes the degradation of superoxide to hydrogen peroxide. If levels of superoxide dismutase are low, nitric oxide reacts with superoxide to form peroxynitrite, which can initiate a cascade of lipid peroxidation reactions. Furthermore, the urate radical (due to increased UA levels) acts as a pro-oxidant under conditions of low ascorbate, causing direct vascular oxidative damage [140].

Although the body is constantly bombarded with the adverse effects of reactive species generations due to many exogenous risk factors such as lifestyle choices and environmental effects (e.g., smoking, alcohol consumption, physical stress), it tends to control the rate of production of free radicals tightly and hence this production does not outwit the rate of UA utilization/elimination. Therefore, if for any reason these defense systems are compromised, pathological conditions manifest due to oxidative stress. Under this condition of oxidative stress, the "protectors" now becomes the "villains," starting a cascade of cellular responses. In diseases such as gout and MS, abnormal levels of UA below and above reference range constitute a primary loss of protection against oxidative stress [102,141]. This loss of protection from oxidative/nitrosative stress one by one exposes the body to chronic adverse health conditions that could be asymptomatic or symptomatic and set the stage for full-blown disease, especially in the presence of other predisposing comorbidities. Such diseases have a potent mechanism through which abnormal serum UA contributes to initiation or progression, although high or low serum UA levels have both risk-predisposing effects as well as biological functions (protection) in conditions such as PD, Alzheimer's disease, stroke, renal disease, gout, and MS.

5. Systemic Consequence of Abnormal Serum UA Levels: The Doubled-Edged Sword

High and low serum UA levels have significant systemic effects. These effects can be explained based on the following assumptions. (1) Exceeding the body's threshold of renal handling of UA results in the oversaturation of its UA carrying capacity, causing systemic overload (a product of defective production and elimination). Armed with the potential to be reactive (especially during prolonged intracellular oxidative challenges), soluble UA exerts negative or positive effects on plasma antioxidant capacity. Depletion of this capacity (owing to the increased circulation of reactive UA, oxygen, and nitrogen species at levels the body cannot handle) opens the door to many metabolic complications that may be occurring in the body but have remained asymptomatic. It is notable that chronic episodes of elevated serum UA are implicated in many defective metabolism-induced complications. (2) On the contrary, owing to the defective production and elimination of UA, low levels of UA may have detrimental effects, especially in neural tissues. Reduced UA along with possible reductions in the levels of supportive antioxidants such as ascorbic acid, compromises antioxidant capacity, leads to a cascade of defects resulting from reoccurring exposure of the body to reactive species and poorly handled oxidative stress.

Viewed from both edges, as a cellular defensive weapon, UA can be an antioxidant or a pro-oxidant depending on the pre-existing cellular environment and demand. In plasma, its antioxidant activities are more pronounced and tend to prevent cellular membrane damage from reactive species-induced oxidative stress and facilitate cell integration and regeneration. Its activities on the cell membrane promote cellular health by scavenging peroxynitrite, superoxide, and hydroxyl ions.

Once UA enters the cell, it can act as a pro-oxidant by losing its antioxidant status due to electron donation to form urate radicals or by stimulating nicotinamide adenine dinucleotide phosphate oxidase [142] and it can induce oxidative stress, stimulate inflammatory mediators, cause endothelial dysfunction, and activate the local renin-angiotensin system. [142,143]. As a double-edged sword, abnormal serum UA levels—both below and above the reference range—confers an increased risk of adverse health effects, as shown in Figs. 2–4.

Abnormally high levels of UA can predispose individuals to or even complicate cardiovascular disease, hypertension, atherosclerosis, hyperinsulinemia, cancers, renal insufficiency, diabetes mellitus, and cerebrovascular events, whereas abnormally low levels of UA can translate to greater oxidative stress and the possibility of developing complications associated with this increased stress. There is evidence for an association between hypouricemia and optic neuritis [144], MS [141], PD [145], and cancers of the upper stomach [15]. Recent evidence has linked hypouricemia with oxidative stress in type 1 diabetes mellitus and EIARF [58, 92]. The link between renal hypouricemia (idiopathic or hereditary) and acute renal failure is postulated to occur via the oxidative stress pathway induced by exercise and UA precipitation. Evidently, FE-UA in hypouricemia is increased (>150%), leading to hyperuricosuria. In a patient studied by Jennin et al [47], FE-UA changed from 200% to 732% between two hospital admissions, with a daily urinary UA excretion of 411 mg. The severe clinical manifestations—low UA and very high FE-UA—that characterized both admissions suggested RHUC.

Although the pathogenesis of EIARF is unclear, three hypotheses have been developed to explain the condition: (1) Acute urate nephropathy due to increased production of UA during physical exercise. (2) Ischemic kidney injury secondary to exercise-induced oxidative stress in the absence of the protective effect of the antioxidant UA [146-149]. (3) Because URAT1 is an anion/urate exchanger, inactivation of URAT1 via loss-of-function mutations in either *URAT1* or *GLUT9* will not only abolish UA absorption but also block the secretion of organic anions to the tubular lumen. The tubular accumulation of toxic urate coupled with the organic anions produced during exercise (such as lactate) may have detrimental effects on renal proximal tubules, leading to acute tubular injury [150]. Most interesting, acute renal failure is evident as a complication in both abnormally high [33] and low. [47,150]. UA levels associated with significant morbidity. This gives credence to the doubled edged sword effects of abnormal uric acid.

Table 3. *A review of possible mechanisms by which abnormal serum UA causes diseases*

HYPERURICEMIA
➢ Acute renal failure via
• *Renal vasoconstriction* (via inhibition of nitric oxide synthase 1), reduction in endothelial cell nitric oxide (via NADPH oxidase in adipocytes and endothelial cells) and stimulation of renin-angiotensin system,
• *Anti-angiogenic properties* (inhibition of endothelial cell apoptosis, which accelerates endothelial cell loss and retards recovery,
• *Pro-oxidant properties* (stimulation of oxidants [via increasing activities of NADPH oxidase] and peroxynitrite-associated radicals [allantoin, 6-aminouracil, and triuret]),
• *Proinflammatory properties* (stimulation of monocyte chemoattractant protein-1; C-reactive protein activation of nuclear factor κB and p38 mitogen-activated protein kinase),
• Alteration of renal autoregulation via development of preglomerular arteriolar disease (linked with systemic glomerular hypertension and cyclooxygenase-2-mediated, thromboxane-induced diseases) [33,142,162-164]
➢ High serum UA in type 2 diabetes mellitus acts via
• Insulin resistance syndrome associated with hyperinsulinemia,
• Impaired glucose tolerance and early onset of overt (diabetic) nephropathy [98,108,165,166].
➢ High serum UA in type 1 diabetes mellitus is linked to overproduction of nitric oxide and oxidative stress [92].
➢ High serum UA can exacerbate chronic kidney disease via endothelial dysfunction, activation of local angiotensin system, increase oxidative stress, proinflammation and proliferation [167,168].
➢ High serum UA is associated with high rates of severe acute respiratory syndrome and COPD, especially among current smokers, linked to inflammatory defects.
• Abnormally high serum UA is associated with acute exacerbation of COPD [169-171].
➢ Increased serum UA is associated with anovulatory cycles linked to follicular development or an underlying endocrine or metabolic disturbance [28].
➢ High UA induces gout via
• Syk and P13K activation, phagocytosis and cytokine production,
• Activation of Toll-like membrane receptors,
• MSU crystal-induced inflammation associated with NALP3 inflammasome activation and IL-1β release [172-174].
➢ High UA is also associated with chronic nonspecific musculoskeletal pain, possibly via
• MSU-induced inflammation,
• Production of prostaglandin and bradykinin and sensitization of nociceptors,
• Release of substance P resulting in vasodilation, plasma extravasations, leucocytes recruitment, mast cell degranulation, and release of prostaglandins and cytokines [172-174].
➢ High serum UA levels may contribute to neurodegenerative disease through activation of the NLRP3 inflammasome via the MSU crystal-NLRP3 inflammasome-IL-1β pathway [1,175-177].
➢ Cardio-renal-metabolic diseases are exacerbated in the presence of high serum UA due to its role in
• Endothelial dysfunction and vascular smooth muscle cell proliferation (via activation of platelet-derived growth factor and mitogen-activated protein kinase) and pre-glomerular arteriopathy,
• Increased oxidative redox stress,
• Fatty acid synthesis and production of NADPH,

- Stimulation of renin-angiotensin system: juxtaglomerular renin production and a decrease in macula densa nitric oxide synthetase expression,
- Hyperinsulinemia and insulin resistance,
- Accelerated atherosclerosis and renal vascular resistance due to vasoconstriction,
- Salt sensitivity and increased sodium reabsorption,
- Leptin interaction [44,162,178-181,183].

➢ High serum UA induces tumor growth and metastasis in cancer cells via

- Activation of NADPH oxidase and generation of ROS in tumor-associated leukocytes and adipocytes leading to proinflammatory stress,
- Downregulation of XOR expression and adiponectin,
- Loss of XOR in most aggressive cancer cells contributing to tumor cell proliferation, migration and survival and progression from early stage to highly aggressive cancer.
- Leptin-related downregulation of cancer cell XOR [24].

➢ The frequent occurrence of hyperuricemia in HIV-infected patients may result from multiple metabolic, immunologic, and pathologic abnormalities characterizing the progression of HIV disease from asymptomatic infection to terminal illness.

- Hyperuricemia complicates the course of HIV disease via
- Prolonged fever due to infection, neoplastic and autoimmune disorders,
- Hypercatabolic state associated with fasting or cachexia,
- Viremia,
- Possible HIV-related loss of mononuclear cells [184].

HYPOURICEMIA

➢ induces Exercise induced acute renal failure via

- Acute urate nephropathy due to increase production of UA during physical exercise,
- Ischemic kidney injury secondary to exercise-induced oxidative stress potentiated by NADPH oxidase stimulation
- Accumulation of toxic urate coupled with organic anions (e.g., lactate) produced during exercise leading to acute renal proximal tubular injury. [47,146,148,150].

➢ Low serum UA in type 2 diabetes mellitus is associated with

- Worse metabolic control,
- Hyperfiltration and late onset of progression to overt (diabetic) nephropathy [182].

➢ Low serum UA contributes to neurodegenerative disease initiation and progression via

- Reduction of antioxidant capacity,
- Induction of oxidative and nitrosative stress and inflammation, which leads to neuronal degeneration and lower survival.[1,175-177]

➢ Low physiological levels of serum UA stimulate mammary cell aggressiveness *in vitro* [24].

Summary: Low serum UA levels in disease entities are most closely associated with high mortality rate, whereas high serum UA levels are associated with high morbidity rate.

[COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IL, interleukin; MSU, monosodium urate; NADPH, nicotinamide adenine dinucleotide phosphate; NLRP3,NOD-like receptor family- pyrin domain containing 3; XOR, xanthine oxidoreductase]

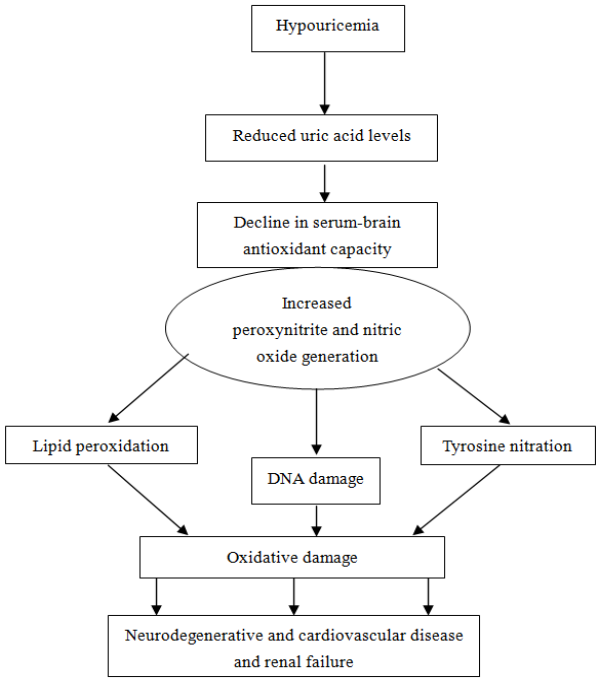

Figure 2. *Cascade of defects associated with hypouricemia: Low levels of serum uric acid (UA) can reduce serum and brain antioxidant capacity. Increased oxidative and nitrosative stress resulting from increased generation of nitric oxide and peroxynitrite causes lipid peroxidation, DNA damage, and tyrosine nitration, ultimately leading to a cascade of defects including neurodegenerative and cerebrovascular diseases and renal failure.*

6. Where Have We Gone Wrong and what Can be Done

Available evidence suggests that man's problems started about 10-20million years ago, when for some reasons, two independent mutations in the uricase gene occurred, impeding the conversion of urate into a more soluble allatoin like in lower animals [151]. The resultant effect is the higher circulatory serum urate level, a situation that predisposes man to increase susceptibility to hyperuricemia and associated complications. The situation became worst when modern humans adopted "risky" health practices in a bid to modify their lifestyles and improve their environment. Consider, for example, our food and water sources. Due to human activities and industrialization during the past 100 years, the pH of the soil has shifted toward acidity. Acidic soils below pH 6 may have reduced calcium and magnesium, and soil with a pH of >7 can have chemically unavailable iron, manganese, copper, and zinc. The addition of dolomite and manure (e.g., animal dung) raises the pH in soil with pH values of <6 [152]. Since the agricultural revolution, the recurring dietary trend is characterized by decreased potassium compared with sodium and an increase in chloride compared with bicarbonate, thereby reversing the K^+/Na^+ ratio [153,154].

Consequently, modern humans have a diet poor in

magnesium, potassium, and fiber and rich in saturated fat, simple sugars, sodium, and chloride compared with that consumed during the pre-agricultural era [154]. This diet might progressively induce metabolic acidosis. With advancing age, renal acid-base regulatory function gradually declines, resulting in an increase in diet-induced metabolic acidosis attributable to the modern diet [155]. A low-carbohydrate, high-protein diet, with its increased acid load, may in fact cause only a slight change in blood chemistry but result in rather significant changes in urinary chemistry, which in turn has negative influences on blood chemistry.

Thus, urinary magnesium, citrate, and pH are decreased; urinary calcium, un-disassociated UA, and phosphate are increased [152]. The alkalinization of urine via an alkaline diet has remained a proposed mechanism for managing musculoskeletal, cardiorenal, and metabolic diseases and accumulated UA loads [76,156], although its potency remains disputed. Various studies have recommended a balanced vegetarian diet with moderate animal protein (meat and fish) and purine content, adequate fluid intake, high alkali loads from fruits, vegetables, and fiber, and moderate alcohol consumption as an improvement over the westernized diet composed of more acid-prone foods such as high animal protein, saturated fats, simple sugars, and alcohol [76,152,156].

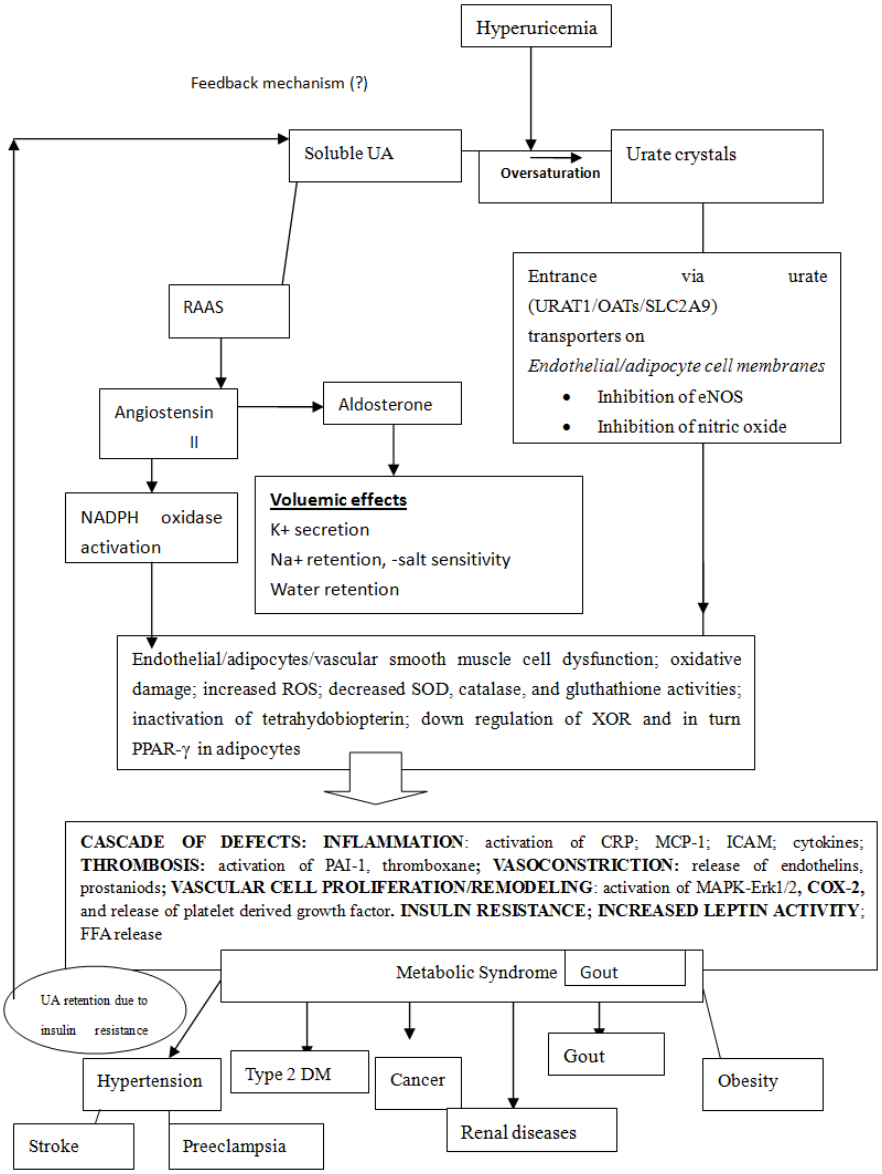

Figure 3. *Cascade of defects associated with hyperuricemia: In hyperuricemia, a high concentration of uric acid circulates in the serum. In conditions of oversaturation due to altered systemic pH, soluble uric acid has the potential to crystallize as monosodium urate in soft tissues or enter target cells and directly or indirectly lead to a cascade of systemic defects including endothelial dysfunction, activation of the local renin-angiotensin system, oxidative stress increase, proinflammation, and proliferation. [COX-2, cyclooxygenase-2; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthetase; FFA, free fatty acid; ICAM, intercellular adhesion molecule-1; MAPK-Erk1/2, mitogen-activated protein kinase-extracellular signal-regulated kinase 1/2; MCP-1, monocyte chemo attractant protein-1; OAT, organic anion transporter; PAI-1, plasminogen activator inhibitor-1; PPAR-γ, peroxisome proliferator-activated receptor-gamma; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SLC2A9, solute carrier family 2 [facilitated glucose transporter] member 9; SOD, superoxide dismutase; URAT, uric acid transporter; XOR, xanthine oxidoreductase].*

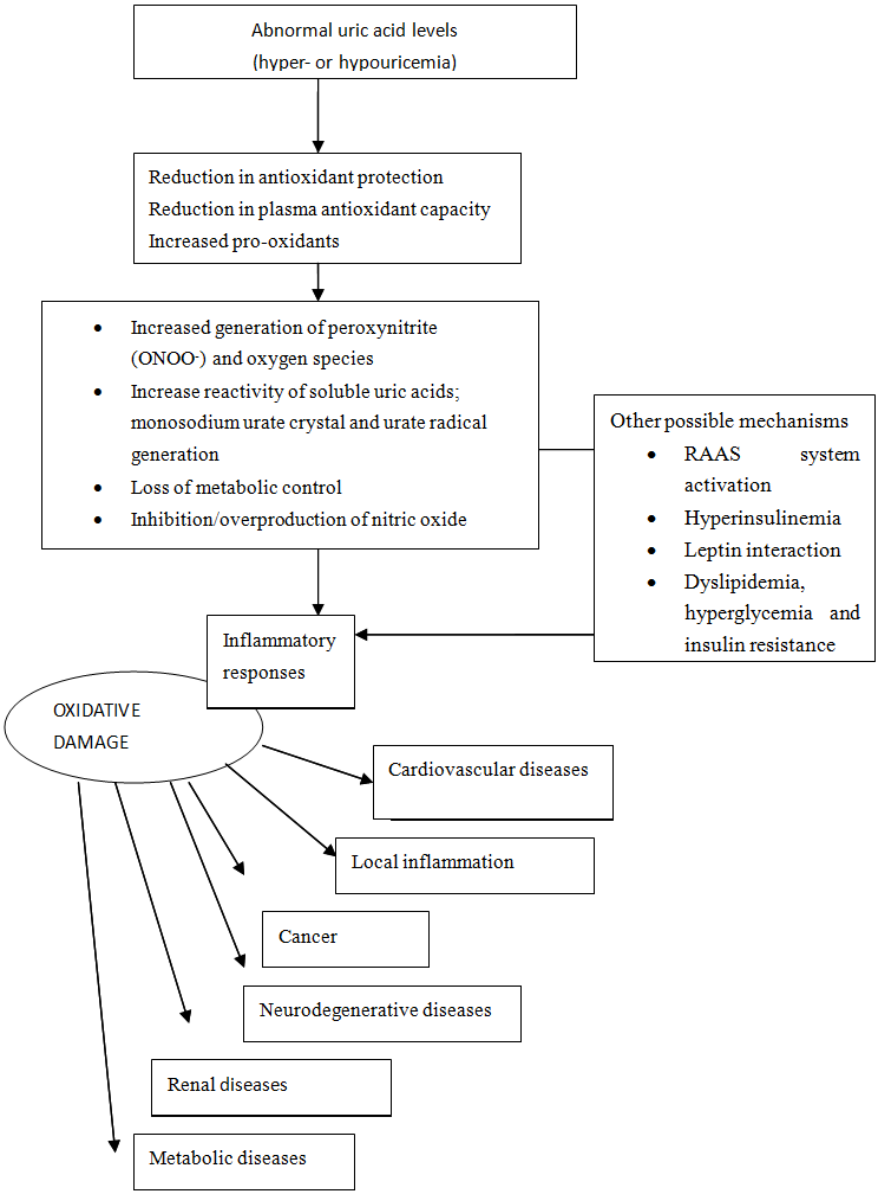

Figure 4. *Proposed mechanism through which abnormal serum uric acid could induce and affect the progression of various disease entities. [RAAS, renin-angiotensin-aldosterone system].*

However, diet may be a confounding factor in the etiology of deranged serum UA levels. Empirically, diet can influence the occurrence of high UA concentrations in that a positive association is observed with high intakes of meat (particularly red meat), fructose, and seafood, and a negative association with the dairy products, coffee, and caffeinated drink intake [102,105,126, 157,158]. Although the consumption of protein, meat, and legumes, which are associated with high purine intake, was unrelated to serum UA concentration in a study by de Oliveira et al [157] because a purine-rich diet was responsible for only 1–2 mg/dL of serum UA [22,159], it is reasonable to suggest that dietary factors associated with metabolic syndrome could indirectly influence urate concentration [158]. Hence, it is worthwhile to advocate healthy eating as an effective and inexpensive way to manage abnormal UA levels. Chronic consumption of diets that increase the odds for derangement in serum UA levels should be discouraged. With advancing age, individuals should check their dietary patterns and avoid overindulgence in risky eating habits and lifestyle choices that predispose them to metabolic deficits. Regular screening of serum UA levels should be conducted. For individuals battling abnormal UA levels (high or low), moderate to regular physical activity and maintaining normouricemia is recommended. Campaigns to raise awareness about the dangers associated with deranged UA levels should be undertaken, especially in developing countries. Clearly, the triad of deranged UA, insulin resistance, and abdominal adiposity are integral to the etiology of many non-communicable diseases in developed and developing countries. In most developing societies, much research on local foods remains to be performed to ascertain whether they promote metabolic deficits.

In addition to the drawbacks introduced by our food sources are those related to water sources. Although it may seem

negligible, water content might have a role in the body's homeostasis. The water consumed by modern humans has been modified and re-modified for absolute cleanliness using various procedures (such as reverse osmosis, alkaline ionization, and distillation). Disputable though it may seem, these processes may have silent adverse effects on the body. These choices are again where we have gone wrong. Human activities have resulted in an increasing incidence of water toxification and pollution such as lead poisoning, which may contribute to the observable increased disease burden. Lead-induced nephropathy is among the factors associated with high serum UA levels (see Table 2). All of the evidence points to derangement in body chemistry, exposure of the body to additional stress through reduced antioxidant status of plasma in which serum UA plays a central role, and lowered resistance to invading disease entities. Abnormal UA (high or low) is a risk factor for morbidity and mortality in certain disease entities [160]. For example, diabetic patients with low serum UA levels associated with hypoalbuminemia have a higher risk of death, likely due to the deadly short-term effects of oxidative stress characterized by hypoalbuminemia, loss of antioxidant effect of low serum UA levels, or both [160]. It could be concluded therefore that as a double-edged sword, abnormal serum UA among other players in any disease entity exacerbates disease conditions because of the increased exposure to oxidative stress (which initiates disease status) and the lowered antioxidant capacity of the plasma (advances disease course); hence, it cuts with both edges (Table 3). UA levels should be considered seriously because (1) subjects with derangement in UA levels are frequently asymptomatic, and (2) the effects of any derangement, although slow at onset, can rapidly progress and become widespread.

7. Conclusion

Consistent data demonstrate that altered serum UA level both markedly below and above the reference range for individual traits and contexts is associated with adverse health effects, a situation referred to as a doubled-edged sword. Specific prevention plans for susceptible individuals should include UA status monitoring and education about derangement management procedures. Regular routine screenings for individuals susceptible to abnormal UA are highly recommended. These individuals include patients with renal impairment, chronic nonspecific musculoskeletal pain, and compromised respiratory, immune, and hemodynamic states; smokers, pregnant women, and patients with medical conditions associated with hyperuricemia (gout, urolithiasis, type 2 diabetes mellitus, stroke, preeclampsia) or hypouricemia (Fanconi syndrome; Wilson disease; folic acid, molybdenum cofactor, and zinc deficiencies; high copper and iron disorders). Individuals with dietary patterns associated with the risk of developing hypouricemia (vegetarian, TPN) or hyperuricemia (high alcohol and seafood consumption, high-fructose syrup consumption) and men and women aged >40 years who may be susceptible to cardiovascular diseases such as hypertension, metabolic syndrome, and diabetes mellitus should be checked routinely for derangement in serum UA levels. Among athletes, routine screening of UA levels as a prerequisite for athletic participation, especially in schools, should be encouraged to prevent complications associated with EIARF among asymptomatic individuals with abnormally low UA levels. Any derangement from normouricemic status can exacerbate a reduction in plasma antioxidant capacity, and the resulting increased oxidative stress potentiates the progression of any existing disease entity, be it neurodegenerative, renal, cardiovascular, metabolic, or cerebrovascular.

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