European Review for Medical and Pharmacological Sciences 2014; 18: 1295-1306

Is it time to revise the normal range of serum uric acid levels?

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Abstract. – The actual reference range of serum uric acid has been assessed according to its variations among healthy individuals. i.e. those without clinical evidence of gout. By this approach, serum uric acid values between 3.5 and 7.2 mg/dL in adult males and post-menopausal women and between 2.6 and 6.0 mg/dL in premenopausal women have been identified as normal in many countries. However, this definition of normal range of serum uric acid in the general population is inevitably influenced by what we consider as "normal", since the absence of gout flares does not necessarily imply the absence of uric acid-related damage. Indeed, a growing body of evidence indicates that silent deposition of monosodium urate crystals as a result of hyperuricaemia may occur and lead to early destructive skeletal changes. In addition, a growing body of evidences demonstrates that uric acid might play a pathophysiological role in many "cardio-nephro-metabolic" disorders, which seems to be independent of the deposition of monosodium urate crystals, since it is evident also for serum uric acid concentrations below the saturation point for monosodium urate. Taken together, these findings strongly suggest to carefully reconsider the concept of "asymptomaticity" for chronic hyperuricemia and to consequently revise the normal range of serum uric acid levels also considering the progressive worldwide increase of circulating levels of uric acid, which could lead to a "shift to right" (i.e. toward higher values) of normal range. In the light of the new scientific knowledge on the pathophysiological role of uric acid in human disease, a threshold value < 6.0 mg/dL (< 360 µmol/L) seems to better identify true "healthy subjects" and should reasonably be considered for all subjects.

Key Words:
Uric acid, Hyperuricemia, Gout, Cardiovascular disease, Renal disease.

Introduction

The prevalence of hyperuricaemia and gout has been growing in Western countries for the last few decades[1,2]. Gout is currently the most prevalent inflammatory arthritis in developed countries, especially in elderly men. Its prevalence is growing also in other parts of the world, such as New Zealand, where it reached 6.4% in 1992[3], or Eastern China, where it reached 1.14% in 2008[4]. More recently a nationwide population-based study by Trifirò et al[5] described an increase of the prevalence of gout in Italy from 0.7% in 2005 to 0.9% in 2009, with a male/female ratio of 4:1. A parallel trend towards an increasing prevalence of hyperuricaemia (serum uric acid > 6 mg/dL) was also observed (8.5% in 2005 vs 11.9% in 2009). However, the prevalence of hyperuricaemia in Italian people was lower than in other countries; indeed, epidemiological data showed an estimated prevalence of hyperuricaemia of 21% in the US general population[6],

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while population-based studies reported a prevalence ranging from 13% to 25% in China[2,4]. This worldwide rise in the prevalence of hyperuricemia and gout may be related to the epidemic diffusion of overweight and obesity[7], as well as the increased consumption of foods rich in purines[8], alcohol[9], and soft drinks sweetened with fructose[10,11]. As a consequence, the mean serum uric acid levels in United States is increased from 3.4 mg/dL in 1920s[12] to 6.25 mg/dL in 1970s[13]. This implies that perhaps it might be more appropriate to define the reference range of serum uric acid levels according to its physiological role and pathophysiological involvement in human diseases, rather than according to the distribution of its circulating levels in the general population.

Metabolism of Uric Acid

Uric acid is the final product of endogenous and dietary purine metabolism. Uric acid is a weak acid with pKa of 5.75 in the blood and 5.25 in the urine. At a physiological pH of 7.4 in the extracellular compartment the reaction uric acid $\leftrightarrow$ urate H^+ is shifted to the right; so the majority of uric acid (about 98%) circulates in the blood as ionised urate. Because of the high concentration of sodium in the extracellular compartment, urate is largely present as monosodium urate, with a low solubility limit of about 6 mg/dL (360 μmol/L)[14,15]. When urate concentration exceeds this limit the risk of monosodium urate crystal formation and precipitation increases. In urine, which is acidified along the renal tubule, urate is converted into the less soluble uric acid[14,15]. Diet urate content is generally rather modest (100-200 mg/day), whereas endogenous uric acid mostly derives from de novo synthesis and catabolism of nucleic acids (500-600 mg/day)[14]. Endogenous urate is mainly produced in the liver and to a lesser extent in the small intestine. Its production depends on the balance between purine ingestion, intracellular de novo synthesis, recycling, as well as xanthine oxidase function at the end of the purine pathway[16]. A relevant cause of overproduction of urate in Western countries is represented by an excess of fructose consumption[10]. This sugar is the substrate of the enzyme fructokinase, which generates fructose-1-phosphate by a process in which a molecule of ATP is consumed and a molecule of ADP and organic phosphate are generated. This enzymatic reaction is almost irreversible: ATP is not regenerated while ADP is converted to AMP, which is a substrate for the generation of uric acid[10]. About two-thirds of the uric acid produced daily are eliminated in the kidney, while about a third is eliminated in the gastrointestinal tract due to the activity of intestinal bacteria[14]. In human kidney, urate handling involves urate glomerular filtration followed by a complex array of reabsorptive and secretory mechanisms taking place in the proximal tubule[17]. Due to its water solubility and low affinity for plasma proteins urate is freely filtered by the glomerulus. At least 90% of the filtered uric acid undergoes active reabsorption in the proximal tubule, and this process is mediated by specific anion transporters, including URAT1[14,17-19]. This uric acid transporter, localized on the apical side of proximal tubule cells, is an important determinant of the reabsorption of uric acid and is the target of uricosuric drugs such as probenecid, sulfinpyrazone and losartan[18,19]. The net result of these processes is the elimination in the urine of 7-12% of the filtered load. Chronic treatment with diuretics can reduce urate excretion, probably through an increased reabsorption in the proximal tubule secondary to volume depletion and/or a competition of diuretics with uric acid for secretory mechanisms at the level of the proximal tubule[20]. This anti-uricosuric effect of diuretics seems to be evident only at doses > 25 mg/day[20]. Less than 10% of cases of hyperuricemia is due to hyperproduction, while the almost totality of cases is due to reduced excretion[14,15,21]. Patients with gout due to increased intake of foods rich in purines are generally poor excreter, since they need urate concentrations 120-180 μmol/L higher than subjects without gout to achieve similar uric acid excretion rates[22].

Biological Ambivalence of Uric Acid

Uric acid was initially considered an inert waste product of purine metabolism able to crystallize at high concentrations, causing gouty arthritis and renal stones[14]. Recent scientific evidences demonstrated that uric acid exerts different biological effects, depending on its chemical microenvironment, including a protective antioxidant activity as well as a dangerous pro-oxidant action[17]. Uric acid alone contributes to about half of the antioxidant capacity of human plasma and its antioxidant properties are comparable to those of ascorbic acid[23]. This molecule is capable of preventing the nitrosylation of proteins induced by peroxynitrite, the peroxidation of lipids and proteins, the inactivation of tetrahydrobiopterin, an essential cofactor of nitric oxide synthase, and

the Cu^{2+}-mediated LDL oxidation[17]. Uric acid also has the ability to prevent degradation of the extracellular superoxide dismutase, a critical enzyme in defending cells from superoxide anion toxicity[24]. Uric acid can also help to preserve sodium retention and blood pressure[25] and, thus, might have played a role in accelerating the development of bipedal locomotion during an evolutionary period in which food was probably scarce and sodium intake low[26,27]. In addition, uric acid might contribute to the development of insulin resistance and mild obesity[28], through its ability to interfere with some actions of insulin by reducing endothelial nitric oxide, as well as to directly act on the adipocyte[29,30], thereby favoring survival during a period of famine or stress. Finally, the increase of serum urate concentration might also have lead to an improvement in reaction time and mental performance that helped man evolution[31,32], or to an amelioration of innate immune function and the ability to ward off infections or tumors[33,34]. This intriguing hypothesis of a survival advantage deriving from increased circulating levels of uric acid is in contrast with the growing bulk of data suggesting a pathophysiological role of this molecule in human diseases. In addition to the well known link between hyperuricemia and gout, a growing body of evidences suggests that hyperuricemia can possibly lead to cardiovascular, renal and metabolic dysfunction[15,35]. From a pathophysiological perspective, *in vitro* and cellular studies demonstrated that, depending on the chemical microenvironment, uric acid may exert pro-oxidant or nitric oxide-reducing effects that may explain the association among hyperuricemia, hypertension, metabolic syndrome, and cardiovascular diseases[35]. Thus, uric acid is a molecule with extremely complex metabolic and biochemical effects that can not be simplistically divided into beneficial or harmful regardless of its microenvironment and, above all, its concentrations in biological fluids[17]. Taken together scientific evidences suggest a sort of "collision" between the trajectory of genetic evolution and that of social evolution in the modern era, mainly because of the shifts in dietary habits brought about by increasing prosperity during the last few decades. In today's societies people consume significantly more meat and fructose, which both generate uric acid. On the other hand, as a consequence of the uricase mutation which occurred in humans and higher primates in mid Miocene[36], humans not only have higher uric acid levels than most other mammals, but they also can not regulate these levels effectively[37,38]. As a consequence, circulating levels of uric acid in the general population are continuously increasing and are nowadays quite higher compared to those observed in primates lacking uricase, who have serum uric acid levels typically in the 3-4 mg/dL range[38]. In addition, uric acid levels in the primitive Yanomamo of southern Venezuela, whose life conditions were likely similar to those of our prehistoric ancestors, averaged only around 3 mg/dL, suggesting that primitive humans had lower uric acid levels than today[27]. In modern age subjects who achieve the highest uric acid levels and develop hypertension, insulin resistance, diabetes mellitus, obesity, and cardiovascular diseases[37] seem to have lost the evolutionary advantage deriving from uricase gene silencing. Thus, due to the marked changes in diet resulting in a dramatic increase in purine- and fructose-rich fooods, increase of serum uric acid levels could represent the expression of a physiological adaptation gone awry in Western societies[27].

Uric Acid and Muscoloskeletal Damage

Gout is the most common inflammatory arthritis in men, although it is often misdiagnosed or recognized late in its clinical course, expecially in elderly subjects, in whom its clinical manifestations may be attributed to osteoarthritis[39]. The pathophysiology of gout includes, in the presence of hyperuricaemia, the intra-articular deposition of monosodium urate crystals, which is responsible for the onset of acute attacks of inflammatory arthritis, possibly leading to chronic arthropathy[14]. Although the formation of monosodium urate crystals in joint fluids mainly depends on the local concentration of urate, it is also influenced by other factors, including articular hydration state, temperature, pH and presence of extracellular matrix proteins such as proteoglycans and collagens[14,40]. Most often monosodium urate crystals are released from preformed deposits in the joints and are coated by protein or polypeptide molecules including IgG antibodies that facilitate phagocytosis[14,40]. Protein adsorption is not, however, an indispensable step for cellular activation, as crystals are able to directly interact with monocyte cell membranes as particles[14,40]. After phagocytosis, crystals activate the NALP3 inflammasoma, a cytoplasmic complex consisting of intracellular immune receptors, thus triggering a typical inflammatory response through release of pro-inflammatory mediators,

such as interleukin 1β and tumour necrosis factor α which in turn, by interacting with specific receptors expressed on synoviocytes, lead to the production of chemokines and the accumulation of neutrophils in the joint[41]. The classic gout flare usually develops after years of asymptomatic hyperuricemia, which represents a possible harbinger of clinical gout, being the incidence of gout directly correlateed to the degree of hyperuricaemia[42]. Furthermore, monosodium urate deposition was demonstrated to occur in any body fluid with a urate level > 6.8 mg/dL[43], and monosodium urate crystals were detected in asymptomatic joints of patients with gout[44]. The presence of monosodium urate crystals in the synovial fluid from asymptomatic individuals with hyperuricemia has been demonstrated by means of polarized light microscopy since early 1980s[45]. Silent deposition of monosodium urate crystals as a result of hyperuricaemia may lead to early destructive skeletal changes: a large percentage of patients with gout and normal radiographs have occult destructive arthropathy detectable by advanced imaging, such as MRI and/or ultrasound[46]. Interestingly, ultrasound evaluation can identify a wide spectrum of subclinical morphostructural changes suggestive of gouty arthritis in both intra- and extra-articular structures in asymptomatic individuals. Pineda et al[47] recently described the typical hyperechoic enhancement of the superficial margin of hyaline cartilage (double contour sign) in 25% of the first metatarsophalangeal joints and in 17% of the femoral cartilage of hyperuricemic asymptomatic individuals (vs 0% in the control group). Patellar and Achilles enthesopathy were also more frequent in hyperuricemic than in normouricemic individuals (12% versus 2.9%; $p = 0.01$ and 15% versus 1.9%, $p = 0.0007$ respectively). The double contour sign has been described in gout only, and reflects the preference of serum urate to crystallize on the surface of cartilage[48,49]. As confirmation of the presence of monosodium urate in the hyaline cartilage, the double contour sign disappears in patients with gout successfully treated with urate-lowering agents, maintaining serum urate levels below the solubility limit of uric acid (< 6 mg/dL) for at least 7 months[50]. Accordingly, the primary therapeutic goal of urate lowering therapy, i.e. promoting crystal dissolution and preventing crystal formation, is achievable by maintaining serum uric acid levels below the saturation point for monosodium urate[51-53]. Long term maintenance of serum uric acid levels below the value of 6 mg/dL results in elimination of gout flares and improvement of tophus status over time[54]. These observations are of great clinical relevance, requiring to carefully reconsider the management of asymptomatic chronic hyperuricemia: although chronically elevated serum urate has not usually been considered to play a pathogenetic role in tissue damage, the ultrasound evidences reported above might warrant the use of urate-lowering agents also in patients with persistent hyperuricemia without clinical signs of gout[47].

Uric Acid and Traditional Cardiovascular Risk Factors

During the last few decades several epidemiological studies have reported a relation between serum uric acid levels and traditional cardiovascular risk factors, including hypertension, metabolic syndrome and diabetes mellitus, suggesting a possible pathophysiologic link between these conditions[55]. In humans, hyperuricaemia is associated with an increased risk of incident hypertension, which is independent of traditional risk factors and more pronounced in younger individuals with pre-hypertension and in women[56,57]. On the other hand, treatment with allopurinol of adolescents with hypertension and hyperuricemia was reported to be associated with a significant reduction compared to placebo in systolic (−6.9 ± 4.4 mm Hg vs −2.0 ± 0.4, $p = 0.007$) and diastolic (−5.1 ± 2.4 mmHg vs −2.4 ± 0.7, $p = 0.03$) blood pressure[58]. Interestingly, the threshold value of serum uric acid associated with hypertension seems to be as low as 5.0-5.5 mg/dL, clearly below its supersaturation value, thus being probably independent of the formation of monosodium crystals[56]. In adolescents with newly diagnosed, never treated stage 1 essential hypertension and serum uric acid levels > 6 mg/dL, reduction of uric acid levels to values < 5 mg/dL with allopurinol therapy was associated with blood pressure normalization in 86% of patients, as compared with 3% with placebo[58].

An elevated serum urate concentration is commonly associated with other components of the metabolic syndrome as well[59]. Although the increase in serum urate has often been considered to be secondary, recent evidences suggest that it may play a pathophysiological role in glucose dysmetabolism[55]. Elevated serum urate levels commonly precede insulin resistance, type 2 diabetes mellitus[60,61], and obesity[62], and studies in cell cultures and animal models have suggested a

causative role for urate in the pathogenesis of the metabolic syndrome. A recent metanalysis of 7 eligible articles derived from 8 prospective cohort studies, involving a total of 32,016 participants and 2930 incident cases of type 2 diabetes, provided strong evidence that high levels of serum uric acid are a risk factor for developing type 2 diabetes in middle-aged and older people, independent of other established risk factors, especially metabolic syndrome components[63]. Interestingly, the presence of only moderately increased serum uric acid levels (> 5.3 mg/dL in women and > 7.0 mg/dL in men) is also associated with a significantly increased risk of developing type 2 diabetes mellitus (hazard ratio: 2.78, 95% CI: 1.35-5.70, $p = 0.0054$)[64]. Pathophysiological mechanisms underlying this association likely include a hyperuricaemia-induced endothelial dysfunction, leading to reduced insulin-stimulated nitric oxide-induced vasodilatation and decreased glucose uptake in skeletal muscle, as well as inflammatory and oxidative changes induced by intracellular urate levels in adipocytes[35,55].

Taken together, these findings suggest a pathophysiological relationship between serum uric acid and traditional cardiovascular risk factors which probably starts below the upper threshold value of serum uric acid currently considered as normal in many countries.

Uric Acid and Cardiovascular Diseases

Epidemiological data support a strong association between gout, hyperuricemia and cardiovascular diseases. The analysis of data from 5926 U.S. participants in the National Health and Nutrition Survey (NHANES I) after a mean follow-up of 16.4 years showed a positive relationship between increased levels of uric acid and cardiovascular mortality; for each mg/dL increase in serum uric acid, cardiovascular mortality increased by 9% in men (HR: 1.09, 95% CI: 1.02-1.18) and 26% in women (HR: 1.26, 95% CI: 1.16-1.36)[65]. Interestingly, the increased risk of fatal cardiovascular events associated to elevated serum uric acid levels was especially evident in older individuals at enrollment[65], suggesting that hyperuricemia must persist for a relatively long time to cause vascular injury, as also observed for traditional cardiovascular risk factors. These findings confirm previous observations in the same population during a survey of shorter duration, demonstrating a mortality from ischemic heart disease 5 times higher among women with serum uric acid > 7 mg/dL compared to women with a serum uric acid < 4 mg/dL[66]. The relationship between serum uric acid levels and cardiovascular events is also evident for moderately increased levels of uric acid or for values corresponding to the upper limit of the actual normal range, as well as for patients with preexisting cardiovascular disease. In the Preventive Cardiology Information System (PRECIS) Database Cohort Study uric acid levels were significantly higher in patients with a diagnosis of coronary artery disease than in individuals with no history of cardiovascular disease (6.3 ± 1.7 mg/dL versus 5.9 ± 1.6 mg/dL, $p < 0.001$)[67]. After 3 year of follow-up, a 39% increased risk of all-cause mortality (95% CI: 1.28-1.50 $p < 0.001$) was evident for each mg/dL increase in serum uric acid[67]. Similarly, in patients with moderate-to-severe heart failure increased levels of serum uric acid were associated with a worse prognosis, with a linear relationship between uric acid levels and probability of death[68]. The presence of deposits of urate crystals represents an important determinant of increased cardiovascular risk in patients with gout. Data from the screening program conducted in Chang Gung Memorial Hospital in Taiwan from 2000 to 2006 clearly indicate that the risk of fatal cardiovascular events was significantly higher in hyperuricaemic patients with gout (HR: 1.97, 95% CI: 1.08-3.59) compared to subjects without gout (HR: 1.08, 95% CI: 0.78-1.51)[69]. Similarly, in the Multiple Risk Factor Intervention Trial (MRFIT) patients with gout showed a higher risk of coronary events (HR 1.35, 95% CI: 1.06-1.72), mortality from myocardial infarction (HR: 1.35, 95% CI: 0.94-1.93), cardiovascular mortality (HR: 1.21, 95% CI: 0.99-1:49) and all-cause mortality (HR: 1.09, 95% CI: 1.00-1.19) compared to subjects without gout ($p = 0.04$)[70]. More recently, the Health Professionals Follow-up Study confirmed the adverse prognostic impact of chronic deposition of urate, demonstrating an increased risk of total mortality (RR 1.28, 95% CI: 1.15-1.41) and fatal coronary events (RR: 1.38, 95% CI: 1.15-1.66) in individuals with a history of gout[71]. These patients also had an increased risk of nonfatal myocardial infarction compared to individuals without gout (RR: 1.59, 95% CI: 1.04-2.41)[71]. According to these findings, Stack et al[72] recently described an independent association of gout and serum uric acid with total and cardiovascular mortality. In particular, mortality risks associated with gout and high serum uric acid levels were

determined for 15,773 participants, aged 20 years or older, in the Third National Health and Nutrition Examination Survey, by linking baseline information collected between 1988 and 1994 with mortality data up to 2006. Compared with subjects without a history of gout, the multivariable hazard ratio for subjects with gout were 1.42 (CI: 1.12-1.82) for total and 1.58 (CI: 1.13-2.19) for cardiovascular mortality. Adjusted hazard ratios for each mg/dL increase in uric acid were 1.16 (CI: 1.10-1.22) for total and cardiovascular mortality and this pattern was consistent across disease categories. In the conjoint analysis, the adjusted hazard ratios for mortality in the highest two uric acid quartiles were 1.64 (CI: 1.08-2.51) and 1.77 (CI: 1.23-2.55), respectively, for subjects with gout, and 1.09 (CI: 0.87-1.37) and 1.37 (CI: 0.11-1.70), respectively, for subjects without gout, compared with those without gout in the lowest quartile. Interestingly, three of the four quartiles of serum uric acid considered in this study were identified by serum uric acid intervals below the threshold of 6 mg/dL (first quartile < 4.3, second 4.3-5.2, third 5.2-6.0 and fourth > 6.0 mg/dL)[72]. These findings are in complete agreement with previous data suggesting that the relation between uric acid and cardiovascular disease is evident not only in the presence of overt hyperuricemia but also with serum uric acid levels considered in the normal to high range (> 5.2 to 5.5 mg/dL)[55,73,74]. The close relationship between hyperuricemia and cardiovascular events is confirmed by some interesting evidences suggestive of a reduction in the probability of developing cardiovascular events associated with the reduction of serum uric acid levels. A post-hoc analysis of data from the Reduction of Endpoints in type 2 diabetes with the Angiotensin II Antagonist Losartan (RENAAL) study demonstrated that each 0.5 mg/dL decrease of serum uric acid observed in the first 6 months of treatment, due to the ability of losartan to interfere with renal reabsorption of uric acid thus enhancing renal excretion, was associated with a 5.3% reduction in the risk of cardiovascular events (95% CI: 0.9-9.9, $p = 0.017$)[75]. This finding suggests the possibility that increased levels of uric acid may represent a modifiable cardiovascular risk factor, at least in diabetic patients with renal disease. In line with these findings is the demonstration of a better cardiovascular prognosis in patients with heart failure[76] or diabetes mellitus[77] treated with high doses of allopurinol compared to those treated with lower doses of this urate lowering drug. These results were recently confirmed by a Scottish study that showed a significant reduction in the risk of cardiovascular events (HR: 0.69, 95% CI: 0.50-0.94) and mortality (HR: 0.75, 95% CI: 0.59-0.94) in patients treated with allopurinol 300 mg/day compared to those assuming 100 mg/day of the same drug[78].

Uric Acid and Brain Health

Increased circulating levels of uric acid have been proposed as an evolutionary advantage for early hominoids due to its potential neurostimulant properties, based on its chemical similarty to caffeine[31]. Several studies described relationships between uric acid levels and IQ testing[79], achievement-oriented behavior[80], and school performance[81], although these associations were generally weak. Despite the intriguing hypothesis that uric acid might have neuroprotective properties, elevated serum uric acid levels are also associated with conditions that increase the risk of cognitive dysfunction. Older adults with high normal concentrations of serum uric acid are 2.7 to 5.9 times more likely to score in the bottom quartile for measures of processing speed, verbal memory, and working memory even after adjustment for potential confounding factors such as age, sex, race, education, diabetes, hypertension, smoking, and alcohol intake[82]. Similarly, in patients with chronic kidney disease, defined by a glomerular filtration rate < 60 mL/min/1.73 m^2, an independent association between circulating levels of uric acid and reduced cognitive performance (r: -0 297, $p < 0.0001$) was described[83]. Furthermore, in the InChianti study, which included a cross-sectional assessment of circulating levels of uric acid and cognitive performance in 1016 community-dwelling elderly subjects, demented patients had higher uric acid levels (5.75 ± 1.90 vs 5.13 ± 1.35 mg/dL, $p < 0.001$) and the prevalence of subjects affected by dementia increased across uric acid tertiles ($p < 0.0001$)[84]. Even after adjustment for possible confounding factors, the highest tertile of serum uric acid was associated with a threefold risk for dementia (OR = 3.32, 95% CI: 1.06 to 10.42), while the intermediate tertile was associated with a higher probability of dementia than the lowest tertile. Interestingly, the relationship between circulating levels of uric acid and dementia was already evident for levels of uric acid essentially below its solubility limit[84]. These findings suggest that the effect of uric acid on cognitive function does not depend on the precipitaion of monosodium urate crystals.

In this regard, Schretlen et al[85] demonstrated that adults with high normal serum uric acid levels are 2.8 times more likely to show greater than average white matter hyperintensity burden, which likely mediates the relationship between serum uric acid and cognitive dysfunction. In another interesting work[86] by the same group performed in community-dwelling adults aged 20 to 96 years, serum uric acid was significantly associated with greater white matter hyperintensities and poorer working memory, processing speed, fluency, and verbal memory. Associations persisted after controlling for age, sex, race, education, hypertension, diabetes, alcohol abuse, smoking, and body mass. The addition of a term for white matter hyperintensity attenuated these associations, in that uric acid no longer predicted cognitive performance[86]. Taken together these findings indicate that severity of cerebral ischemia might mediate the association between uric acid and cognitive dysfunction. Even more interestingly, circulating levels of serum uric acid in this study population were quite low (4.5 ± 1.4 mg/dL)[86]. Thus, also mild elevations in uric acid appear to contribute to structural and functional brain changes. A growing body of evidence indicates that serum uric acid is also an independent predictor of stroke[87]. Storhaug et al[88] recently demonstrated in a 12-15 year prospective study on 5700 men and women free of diabetes and cardiovascular diseases, that each 1 SD (1.5 mg/dL) increase in serum uric acid was associated with a 22% increased risk for ischemic stroke and a 13% increased risk for all-cause mortality. Taken together, the above data indicate that serum uric acid might have a detrimental impact on brain vasculature and consequentely, on brain structure and function.

Uric Acid and Renal Disease

Experimental studies suggest the possibility that an elevated concentration of uric acid itself can lead to kidney disease without the deposition of uric acid crystals[89,90]. Animal studies demonstrated that experimental hyperuricaemia obtained through inhibition of uricase can cause de novo kidney disease, as well as accelerate existing renal dysfunctions[89,90]. The main lesions caused by increased uric acid in the rat are glomerulosclerosis, interstitial fibrosis, and arteriolar disease, conditions similar to those observed in "gouty" nephropathy, except for the absence of intrarenal urate crystals[89,90]. The mechanism of injury appears to be related to the development of preglomerular arteriolar disease that impairs the renal autoregulatory response and thereby causes glomerular hypertension[91]. In humans a number of cross-sectional studies found an association between urate levels and decreased estimated glomerular filtration rate or microalbuminuria, although the interpretation of these findings is difficult, since chronic kidney disease can elevate urate levels, and hyperuricaemia might cause or aggravate chronic kidney disease. Focusing on incident chronic kidney disease, most studies showed an independent association with serum urate levels. However, the analysis of the progression of chronic kidney disease and its relationship to urate levels gave conflicting results, most studies finding no independent association with hyperuricaemia. This could indicate that urate is a risk factor for the onset of chronic kidney disease more than for its progression[92]. However, a recent review supports the role of urate as a risk factor for chronic kidney disease[93]. The evidence that the reduction of serum uric acid concentration might favorably affect the clinical course of kidney disease further supports the hypothesis of a detrimental role or uric acid on renal function. Siu et al[94] demonstrated that 12 months allopurinol treatment decreased systolic blood pressure (from 140 to 127 mmHg) and slowed chronic kidney disease progression. Goicoechea et al[95] described a favorable effect of allopurinol on estimated glomerular filtration rate decline (defined as a decrease of > 0.2 mL/min/1.73 m^2; adjusted HR: 0.53) and a beneficial effect on cardiovascular endpoints (7/57 versus 15/56), but no effect on blood pressure. Momeni et al[96] described a reduction in proteinuria (from 1.8 to 1.0 versus 1.7 to 1.6 g/24 h) after allopurinol treatment in patients with type 2 diabetes mellitus and diabetic nephropathy. In IgA nephropathy patients Shi et al[97] described a reduction of the antihypertensive drug doses in 7/9 cases with hypertension during 6 months allopurinol treatment versus 0/9 in the control group. In a posthoc analysis of the Reduction of Endpoints in type 2 diabetes with the Angiotensin II Antagonist Losartan (RENAAL) trial, losartan reduced urate levels by 0.16 mg/dL from 6.7 mg/dL during the first 6 months; adjustment for the urate effect indicated that 1/5 of losartan renoprotective effects could be attributed to this reduction in urate[98]. Taken together, the above findings suggest an influential role of serum uric acid on renal function, which likely starts below its solubility limit, being independent of monosodium urate crystals deposition.

Is it Time To Revise the Upper Threshold for Serum Uric Acid Levels?

In health-related fields, a reference range usually describes the variations of a measurement or value in healthy individuals. In particular, the standard definition of a reference range for a particular measurement is defined as the predicted interval including 95% of values of a reference group, in such a way that in 2.5% of cases a sample value will be smaller than the lower limit of this interval, and in 2.5% of cases it will be larger than the upper limit of this interval, whatever the distribution of these values. By this approach, serum uric acid values between 3.5 and 7.2 mg/dL in adult males and postmenopausal woman and between 2.6 and 6.0 mg/dL in premenopausal women have been identified as normal in many countries. However, epidemiological and experimental data accumulated during the last few decades suggest that this methological approach to identify reference range could present some weaknesses when applied to serum uric acid levels. Indeed, epidemiological data suggest a progressive worldwide increase of circulating levels of uric acid, which could lead to a "shift to right" (i.e. toward higher values) of normal range. Thus, it seems reasonable to redefine the normal threshold values of uric acid according to its physiological role and its pathophysiological involvement in human diseases. Regarding the target population, healthy subjects are likely to be represented by individuals without clinical evidence of gout. However, a number of evidences suggest that articular damage may occur also without clinical evidence of acute artritis. In addition, the growing body of evidences presented above suggests that serum uric acid might also exert a detrimental influence on cardiovascular system, brain and kidney and negatively influence glucose metabolism. Interestingly, this influence seems to be evident also for circulating levels of uric acid below its saturation limit, indicating that it is likely independent of precipitation of urate monosodium crystals. Thus, the defintion of normal range of serum uric acid in the general population is inevitably influenced by what we consider as "normal", since the absence of gout flares does not necessarily imply the absence of uric acid related damage. On the other hand, there are also "optimal health ranges" identifying the optimal health impact on people. This might be the case for uric acid, since a threshold value < 6.0 mg/dL (< 360 μmol/L) seems to better identify true "healthy subjects". Moreover, from an analytical perspective, considering that desirable analytical goals for imprecision and bias should be 4.3% and 4.8%, respectively[99], for a threshold of serum uric acid concentration of 6.0 mg/dL the imprecision should not exceed 0.26 mg/dL, giving a range of uncertainty between 5.74 and 6.26 mg/dL, i.e. substantially below the solubility limit of uric acid. Therefore, in the light of the new scientific knowledge on hyperuricemia, the recommendable upper threshold value for serum uric acid should reasonably be considered < 6.0 mg/dL. This methodological approach could represent also a strategy to sensitize clinicians towards clinical problems now recognized to be related to uric acid.

Conclusions

Gout is one of the earliest disorders recognised as a clinical entity, which has been associated since its first description to a state of socioeconomic welfare. During the last years, gout has gained renewed interest by clinicians mainly because its continously increasing prevalence, which is likely to be greater than the epidemiology of "podagra" could suggest. Indeed, radiological evidences demonstrate a wide spectrum of subclinical morphostructural skeletal changes, suggesting that articular damage induced by hyperuricemia can occur in both intra- and extra-articular structures in asymptomatic individuals. These data open a new battlefront in the current debate about the opportunity to maintain serum uric acid levels below the threshold value of 6.0 mg/dL (360 μmol/L) also in these subjects as already recommended for patients with overt gouty arthritis[51-53]. In addition, a growing body of evidences demonstrates that uric acid might play a pathophysiological role in many "cardio-nephro-metabolic" disorders, which seems to be independent of the deposition of monosodium urate crystals, since it is evident also for serum uric acid concentrations below the saturation point for monosodium urate. Taken together, these findings strongly suggest to carefully reconsider the concept of "asymptomaticity" for chronic hyperuricemia and to consequently revise the normal range of serum uric acid levels. A threshold value for serum uric acid < 6.0 mg/dL (< 360 μmol/L) should reasonably be considered for all subjects.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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