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Review

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Is there anything good in uric acid?

B. ÁLVAREZ-LARIO[1] and J. MACARRÓN-VICENTE[2]

From the [1]Rheumatology Department and [2]Neurology Department, Complejo Asistencial Universitario, Burgos, Spain

Address correspondence to B. Álvarez-Lario, Sección de Reumatología, Complejo Asistencial Universitario de Burgos, Avda. del Cid 96, 09005 Burgos, Spain. email: balario@hgy.es

Summary

High uric acid (UA) levels can cause gout, urolithiasis and acute and chronic nephropathy, all of which are due to the deposit of urate crystals. There is also increasing evidence of relationships of hyperuricemia with other important disorders, including hypertension, chronic renal disease, metabolic syndrome and cardiovascular disease, as well as an increased mortality, although a causal relationship between these conditions has not been clearly established. On the other hand, low UA levels are not known to cause any disorder or disease. However, in the last few years a higher prevalence and progression of some neurological diseases have been associated with a low UA, and it is possible that they may predispose to some other disorders, mainly due to the decrease in its antioxidant activity. In this article, the known negative effects of UA are reviewed, as well as the much less-known possible positive actions, and their therapeutic implications.

Introduction

Uric acid (UA) is the end product of purine metabolism in humans, unlike other mammals where UA is metabolized to allantoin by uricase (Figure 1). The amount of UA in blood depends on the ingestion of purines in the diet, the biosynthesis of UA from endogenous purines and renal balance, where up to 90% of the filtered UA is reabsorbed[1] (Figure 2). UA regulation is complex, with the main causal factors of hyperuricemia being, diet, different genetic polymorphisms of renal urate transporters, as well as the inactivation of uricase by various mutations of its gene during the evolution of hominids, which causes UA levels to be up to 10 times higher in humans than in other mammals.[1,2]

High UA levels can cause gout, urolithiasis and acute and chronic nephropathy, all of which are due to the deposit of urate crystals. There is also increasing evidence of relationships of hyperuricemia with other important disorders, including hypertension, chronic renal disease, cardiovascular (CV) disease and metabolic syndrome,[1,3] although a causal relationship has not been clearly established.

Low levels of UA are not a known cause of any disorder or disease. However, in the last few years a higher prevalence and progression of some neurological diseases[4–6] have been associated with low UA levels, and it is possible that they may predispose to some other disorders, mainly due to the decrease in its antioxidant activity.[2]

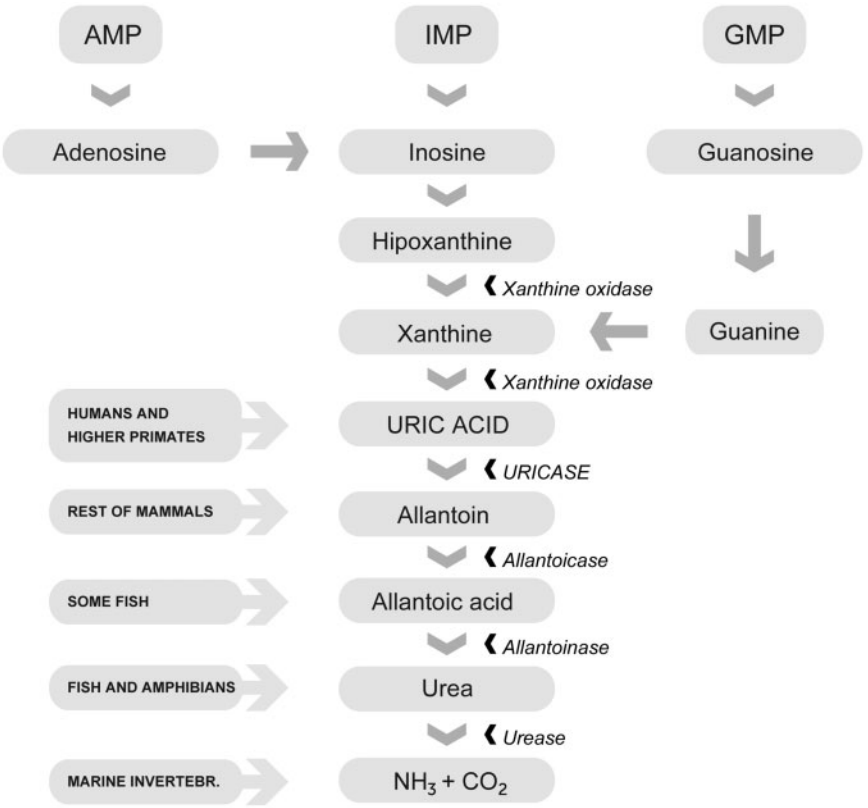

Figure 1. Schematic representation of purine metabolism. UA is the end product of purine metabolism in humans and in some higher primates, due to the lack of uricase. In the large majority of mammals, UA is converted by uricase to allantoin, a very soluble excretion product that is freely eliminated in the urine. In the majority of fish and amphibians, the allantoin formed is degraded to urea and glyoxalate, via allantoic acid, by allantoicase and allantoinase. In some marine invertebrates and crustaceans, the urea formed is hydrolyzed to NH_3 and CO_2 by urease. AMP: adenosine monophosphate; IMP: inosine monophosphate; GMP: guanosine monophosphate.

In this article, we review the many harmful associations of UA, as well as the few possibly beneficial ones, and their therapeutic implications.

Harmful effects

Gout

Gout is a rheumatic disease characterized by high levels of UA in blood and UA crystal deposits in the joints. It affects 1–2% of adults in developed countries, being the most common inflammatory arthritis in males and women of advanced age. Epidemiological data indicate that its prevalence is increasing.[1]

Hyperuricemia is a primary risk factor for the development of gout, although it is likely that two–thirds or more of hyperuricemic individuals will remain asymptomatic. This risk increases exponentially as the serum UA levels increase. Thus, subjects with UA levels between 7.0 (416 μmol/l) and 8.0 mg/dl (475 μmol/l) have an accumulated risk of 3% of developing gout, while those with UA levels of 9.0 mg/dl (535 μmol/l) or more have an accumulated risk of 22%.[7]

Urolithiasis

Hyperuricemia and gout are independent risk factors of nephrolithiasis, not only for UA stones, but also for the more common calcium oxalate stones. The prevalence of calcium oxalate nephrolithiasis in patients with gout is 10–30 times higher than that in individuals without gout, which could be due to an increased urinary excretion of calcium and a decreased excretion of citrate.[8]

The risk of developing urolithiasis is higher in those patients with high urinary UA levels and persistently acid urine which favours the precipitation of UA.[9] In primary gout, the incidence of stone formation varies with the UA excretion rate, from 10% to 20% when urinary UA excretion is normal, and up to 40–50% when the renal excretion of UA exceeds 1000 mg/day.[10]

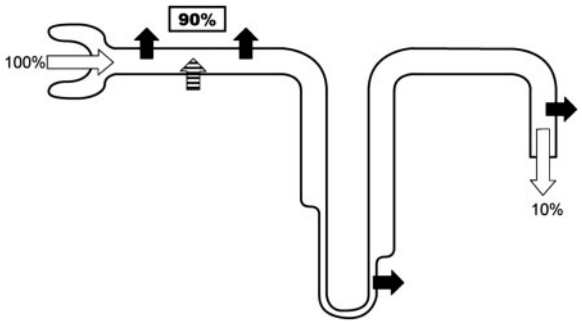

Figure 2. Schematic representation of the renal balance of UA. Less than 5% of UA circulates bound to proteins; therefore, practically 100% is filtered in the glomeruli. Almost all the filtered UA is reabsorbed in the proximal tubule (first black arrow). This reabsorption is then followed by tubular secretion (striped arrow) which returns ~50% of the filtered urate to the tubular lumen and which is the source of the majority of urate excreted. However, the majority of secreted urate is subjected to post-secretory reabsorption (next black arrows), which means that, altogether, ~90% of the filtered urate is reabsorbed.

UA and renal function

UA can cause acute and chronic nephropathy due to direct renal damage. The acute nephropathy due to UA is a result of its precipitation within the renal tubules. It has mainly been described in tumour lysis syndrome or in conditions with a large production and/or an excessive secretion of UA, as in Lesch–Nyhan or Fanconi syndromes. Chronic nephropathy due to urate is a form of chronic renal disease induced by deposits of sodium urate crystals in the renal medullary interstitium, which produces a chronic inflammatory response with interstitial fibrosis and chronic renal damage.[11] Before the use of effective UA lowering treatments, renal impairment was found in up to 40% of patients with gout, with renal failure finally being the cause of death in 18–25% of these cases. It is currently thought that this type of nephropathy is uncommon and should be suspected in patients with hyperuricemia out of proportion to the degree of renal insufficiency.

To establish another causal relationship of hyperuricemia with chronic renal disease besides the previously mentioned nephropathies has been controversial due to the many possible confounding variables. Any decrease in renal function is associated with an increase in UA levels since it is mainly removed by the kidney.[12] Also, the possible associated lithiasis may cause renal damage due to repeated infections and obstruction, and increased UA levels may be involved, as we will see later, in the development of other risk factors of renal disease such as, hypertension, CV disease and diabetes.[12] However, various studies have suggested that hyperuricemia may be an independent factor of renal damage, probably due to microvascular changes.[13] Thus, it has been observed that increased UA levels are a significant risk factor of chronic renal disease, only exceeded by the presence of proteinuria and age.[14] UA levels >7 mg/dl (416 μmol/l) multiply the risk of end-stage renal disease by four in men and by ten in women.[15] Moreover, an improvement in creatinine clearance,[16] and possibly a slower progression of the renal damage,[17] has been observed in hyperuricemic patients treated with alopurinol.

A recent study suggests that uromodulin (UMOD) might play a role in the relationship between gout and chronic renal disease.[18] Mutations in the UMOD gene cause UMOD-associated kidney disease, characterized by hyperuricemia (resulting from reduced kidney excretion of UA), gout, tubulointerstitial nephropathy and end-stage renal disease. It is controversial whether the progress to renal failure is prevented by allopurinol therapy.[19,20]

UA and hypertension

Historically, it had been thought that hyperuricemia was a secondary response to hypertension, which can produce an increased UA by various mechanisms, particularly by an increase in the renal reabsorption of UA due to reduction in renal blood flow.[21] However, more recent clinical and experimental studies show that hyperuricemia *per se* may lead to the development of hypertension. Thus, in rats that were made hyperuricemic by administering a uricase inhibitor, it was observed that they developed hypertension a few weeks after the increase in UA levels, with the blood pressure levels correlating directly with serum UA levels. The blood pressure levels decreased on reducing UA levels with a xanthine oxidase inhibitor or a uricosuric drug.[21] In this model, it was demonstrated that the hypertension was due to renal vasoconstriction mediated by UA, with a reduction in endothelial nitric oxide levels, activation of the renal-angiotensin system, and damage induced by oxidative stress.[21]

Hyperuricemia is associated with an increased risk of developing hypertension in the following 5 years, regardless of other risk factors.[22] The fact that hyperuricemia precedes the development of hypertension indicates that it is not simply a consequence of this. High levels of UA have also been observed in 40–60% of patients with untreated essential hypertension, and in almost 90% of adolescents with recent onset essential hypertension.[23] The strength of the relationship between UA levels and hypertension decreases as the age of the patient

increases and with duration of the hypertension, suggesting that UA may be more important in young people with recent onset hypertension.[24] Two recent meta-analyses concluded that hyperuricemia was associated with an increased risk of hypertension,[25,26] regardless of the traditional risk factors,[26] and was more pronounced in women and young people.[25,26]

On the other hand, treatment with allopurinol returns the blood pressure to normal in young patients with hyperuricemia and hypertension, with the decrease in pressure being similar to that achieved with hypotensive drugs. In adolescents in whom the UA levels fall to below 5 mg/dl (297 μmol/l), ~90% achieve a normal pressure, compared to 3% treated with a placebo.[23] However, for other authors, these data do not necessarily imply a causal relationship of UA with hypertension. The beneficial effect of allopurinol on hypertension in adolescents might be due to the beneficial actions of the allopurinol itself, which, on inhibiting xanthine oxidase, produces a reduction in oxidative stress and endothelial dysfunction, effects that are independent of its UA lowering action.

UA and metabolic syndrome

The hyperuricemia associated with metabolic syndrome has traditionally been attributed to insulin resistance and the hyperinsulinemia of this condition since insulin reduces the renal excretion of UA, which has led to thinking that hyperuricemia is an epiphenomenon in metabolic syndrome. However, recent studies have shown that hyperuricemia leads to obesity, diabetes and even hyperinsulinaemia.[27,28] Also, non-overweight people with hyperuricemia have a higher risk of having an metabolic syndrome. Thus, in a study with subjects with a normal body mass index, only 5.9% of those who had a UA <6 mg/dl (357 μmol/l) had metabolic syndrome, compared to 59% of those with a UA >10 mg/dl (595 μmol/l).[29] On the other hand, it has been observed, in animal models, that the decrease in UA levels with xanthine oxidase inhibitors can prevent or reverse the signs and symptoms of metabolic syndrome.[30]

Hyperuricemia is an integral part of metabolic syndrome, along with hypertension, obesity, dyslipemia and insulin resistance, and various epidemiological studies have demonstrated that metabolic syndrome prevalence increases substantially with increasing levels of UA and vice versa.[29,31] Similarly, the strong association between gout and metabolic syndrome has been demonstrated in several studies that have observed a high prevalence of metabolic syndrome in patients with gout, always higher than the controls, with percentages varying between 30% and 80%, depending on the population groups and criteria used.[31]

UA and CV disease

In epidemiological studies, it has been observed that increased UA levels are an independent CV risk in high risk groups, such as patients with hypertension, congestive heart failure and/or diabetes, as well as in the general population.[32] However, other authors question the role of UA as an independent marker of CV risk. Thus, experts from the Framingham Heart Study Group have demonstrated that UA is not a risk factor of CV disease, and that the clinical analysis should only be based on the classic risk factors.[33] Elevated serum UA could be a marker of underlying tissue ischaemia,[34] and a large part of the risk associated with hyperuricemia could be linked to its inexorable association with other risk factors, especially hypertension.[26]

Two meta-analyses have recently been published on the risk of coronary disease[35] and cerebrovascular disease[36] in patients with hyperuricemia, observing that this only marginally increased the risk of coronary events[35] and modestly increased the risk of stroke.[36] Similarly, in the MRFIT study, it was observed that the association between hyperuricemia and CV disease was weak and did not persist when the analysis was limited to men with hyperuricemia without a diagnosis of gout.[37] Although the MRFIT study was conducted on men with a high risk of CV disease, and the results could not be applied to women or the general population, it suggests that the increase in CV risk could be related more to the presence of gout than to isolated hyperuricemia.[37] The inflammatory process associated with gout during acute attacks, and the sub-clinical inflammation due to the presence of urate crystals in the body, would favour arteriosclerosis and thrombogenesis, as happens in other inflammatory diseases like rheumatoid arthritis or systemic lupus erythematosus.[37] These changes could be additional to the previously mentioned effects of hyperuricemia on endothelial dysfunction and oxidative stress, and independent of other traditional risk factors.[38]

UA and mortality

Epidemiological studies in the past 10 years have found an independent association between hyperuricemia and mortality by all causes and CV mortality.[32,39] Chen *et al*. observed that total mortality due to CV disease increased by 11% for each 1 mg/dl (60 μmol/l) increase in serum UA levels.[32] A serum UA level of >7.0 mg/dl (416 μmol/l) was an independent factor of mortality by all causes, CV

mortality and mortality due to ischemic stroke, after adjusting for classic CV risk factors.[32]

However, the findings have not been so clear in other studies. Thus, an association has been mentioned between hyperuricemia and all mortality causes, but not CV mortality[40] or sex differences had been observed. In the double study, in men and women, by Strasak *et al.*, [41,42]an increase in mortality due to congestive heart failure and stroke was found in men and women with an increased UA, but only the women had a higher mortality due to coronary disease. Other studies have also observed a higher risk of death due to CV and coronary disease in women,[32,35] leading to the possibility that hyperuricemia in women could be a marker of the loss of CV protection of the estrogens.[32]

Other studies have also questioned the association of isolated hyperuricemia with mortality by all and/or CV causes, on not finding any association[33]or this being very weak, with a clearer association only being seen in the presence of gout.[37,43] Patients with gout, compared to those without gout, have a higher risk of total mortality, of death due to CV disease, and fatal coronary disease. The risk of CV mortality was even higher than in patients with a history of coronary disease.[38]

Possible beneficial effects

UA is the end product of purine metabolism in humans and in other higher primates, on lacking the enzyme uricase (Figure 1) due to various mutations in its gene rendering it non-functional.[44] Thus, UA levels in developed countries are ~6.0 mg/dl (357 µmol/l), compared to the majority of mammals, which have UA levels <0.5–1 mg/dl (30–60 µmol/l).[45,46] These mutations have been interpreted as clear evidence of an important evolutionary advantage for the early primates that had increased UA levels.[44] Furthermore, the degradation of purines is much less complete than in other animals that are considered inferior, and it is assumed that it provided us with some evolutionary advantage (Figure 1). On the other hand, if UA was a waste or harmful product, it poorly explains why our kidneys recover 90% of filtered UA,[47] instead of eliminating it (Figure 2). There is a great variation between different mammals in the renal handling of UA, from net secretion with UA clearances two to three times the glomerular filtration rate, as in the pig and some rabbits, down to man, who has a net reabsorption of UA in the renal tubule higher than any other mammal except closely related pimates.[48]

These facts indicate that evolution and physiology have not treated UA as a harmful product, but as something beneficial that has to be preserved, which has led to various researchers to think of the possible evolutionary advantages of the increase in UA levels. For example, one hypothesis associates the increase in UA to the higher intelligence of humans.[49] For other authors, the loss of uricase and the increase in UA could be a mechanism to maintain blood pressure in times of low salt ingestion,[46] which would have been essential so that the hominids could maintain their upright position.[50] However, the biological reason for increased UA levels to occur during human evolution is not clear.[2] It could be that the increase in UA levels from such low values as 0.5 mg/dl (30 µmol/l) to, for example, 2 mg/dl (120 µmol/l) could have provided some benefits to hominids that are currently not well known. A more important increase in UA levels, probably very recent in the evolutionary process, mainly related to the Western diet, could be the cause their current harmful effects.[51] At present, the more recognized beneficial effects of UA are their antioxidant, neuroprotective and immune/inflammatory actions.

UA and antioxidant capacity

Oxidative stress is associated with various physiological and pathological conditions, including CV diseases, neurological diseases, aging and cancer.[52] UA is one of the most important antioxidants in human biological fluids and is responsible for neutralizing >50% of the free radicals in human blood.[52] For this reason, it was thought that the antioxidant effects of UA could increase the life expectancy and/or reduce the incidence of malignancy.[45]

Although there are data that support the role of oxidative stress in aging of invertebrate organisms, the evidence in mammals is less clear, as shown in murine models in which modification of their antioxidant capacity is not associated with changes in their life expectancy.[53,54] Nor is there evidence that people with increased UA levels live longer. In fact, as mentioned previously, patients with hyperuricemia and gout have a higher risk of death by all causes and by CV disease.[32,38,43] Similarly, studies suggest that hyperuricemia does not offer protection against tumours, but rather quite the opposite[55] and that it increases the risk of death due to cancer.[55,56] The same is true in with patients with gout, who have an increased incidence of cancer[57] and a higher risk of death due to malignancy,[43] although the increase in carcinogenesis is probably not due to UA, but rather reflects a lifestyle with an increased risk of tumors.[55]

We are faced with the paradox of UA being a recognized antioxidant; however, increased UA levels are a risk factor for CV disease, in which oxidative stress has an important pathophysiological role.[52,58] UA, besides being a notable antioxidant, also has pro-oxidants actions from the urate radical, or through stimulating the synthesis of proinflammatory molecules, or from xanthine oxidase, which generates free radicals in its enzyme activity.[52] The previous data suggest that in aging, malignancy and CV diseases, the pro-oxidant effects of UA are predominant over the antioxidants, although it may also be possible that hyperuricemia represents a compensatory or protective mechanism to try to prevent or correct oxidative damage.

UA and neuroprotection

The brain is unique with regard to its great vulnerability to oxidative damage due to its high metabolic rate, using a fifth of the oxygen we inhale every day, and which contains lipid material with a high content of unsaturated fatty acids.[59] Therefore, the antioxidant defence mechanisms against lipid perodixation in the brain could be of great importance and that the relationship between UA levels, as a power antioxidant, and these diseases could reflect the neuroprotector action of UA.[60]

Patients with multiple sclerosis have significantly lower serum UA levels than healthy subjects,[6,61] and these levels are lower in the active phases of the disease.[61,62] Serum UA could be used as a marker of the activity of the disease and the response to treatment.[62] On the other hand, it has been observed that gout and multiple sclerosis are mutually exclusive, as such that there have been no reported cases of patients who suffer from multiple sclerosis and gout.[59] Moreover, some studies have found a therapeutic use of the increase of UA with inosine in animal models as well as in patients with multiple sclerosis.[63]

Similarly, it has been observed that UA levels in the serum of patients with Parkinson's disease are lower than in controls and that increased levels of UA are associated with a lower risk of Parkinson's disease,[64–66] although this association was not observed in women.[67] Furthermore, higher levels of UA in serum and cerebrospinal fluid are associated with a slower progression[60] and lower cognitive impairment;[68] therefore, UA could be of value as a marker of the progression of the disease.[60] It has also been observed that diets with a high purine content in Parkinson's disease are associated with a lower risk of the disease and slower progression of the symptoms.[4]

Patients with Alzheimer's disease have a significantly reduced UA and other antioxidant levels when compared to healthy controls,[5] and increased levels of UA seem to be associated with a slower progression of cognitive impairment.[69] The use of oral supplements of ascorbic acid along with precursors of UA, such as inosine or hypoxanthine, could also attenuate the progression of Alzheimer's disease.[70] On the other hand, it has been observed that high levels of UA are associated with a higher probability of dementia syndrome in general.[71] Hyperuricemia has been associated with diabetes, hypertension and ischemic lesions of the white matter, all of which are risk factors for cognitive impairment,[69] with the severity of the cerebral ischemia being that which could modulate the association between UA levels and cognitive dysfunction.[72]

Data on the prognostic value of serum UA levels in stroke are contradictory, with high levels being associated with a poor,[73] as well as a better outcome.[74,75] These findings may be explained by the dual action of UA. On the one hand, hyperuricemia could, as already mentioned, increase the risk of CV disease, while the antioxidant effects of UA could be beneficial in acute ischemia by slowing down oxidative stress and neuron damage.[76] Thus, UA administered to rats 24 h before middle cerebral artery occlusion or 1 h after reperfusion, reduces ischemic damage, with a reduction in the size of the cerebral infarction and better neurological function,[77] which has led some researchers to suggest treatment with UA in stroke.[78]

Finally, a decrease in serum UA levels has also been observed, as well as a relationship with the progression of the disease in patients with amyotrophic lateral sclerosis[79] and Huntington's disease,[80] and the beneficial effects of UA as a neuroprotector in murine models of a spinal cord lesion have been reported.[81]

In summary, there is epidemiological evidence to suggest that low UA levels are associated with an increased risk and progression of some neurological diseases.[58] However, it is controversial whether UA is beneficial *per se* in these diseases or just an innocent bystander.

UA and activation of immune and inflammatory responses

In recent years, UA has also been recognized to have an important role in innate immune responses. In contrast to the acquired immune system, innate responses orchestrate the immediate and early phases of host defence to microbes as well as to injury, initiating the inflammatory reaction

and recruiting cells of the acquired immune system to the site of inflammation.[82] Microcrystalline UA is an endogenous danger signal that activate cellular defences of the innate immune system[82,83] and that acts as a natural endogenous adjuvant.[83,84] Adjuvants enhance the immune response to an antigen and they are widely used in vaccination.[85] Detection and intake of UA crystals by phagocytes, such as monocytes and macrophages, represent the first step in the inflammatory cascade initiated by UA. In phagocytes, UA crystals have also been shown to trigger other stress signals, including generation of free radicals, potassium efflux and cathepsin B release from fractured lyposomes.[85] All these signals may be a key in the activation of the inflammasome, a cytosolic complex that detects pathogens as well as danger or stress signals.[83,85]

Since UA is a ubiquitous metabolite that is produced in high quantities upon cellular injury, the ramifications of its effects may be considerable in health and in disease.[83] Theoretically, activation of the innate immune system and inflammation might be beneficial in fighting infections[86] and other injuries.

Conclusion

UA is not only a waste product of purine metabolism or an inert compound, as has been believed historically, but also has an important role in many biological functions. Although UA is a powerful antioxidant, it also acts as a pro-oxidant giving rise to an increase in free radicals, endothelial vascular dysfunction, inflammation, changes in nitric oxide production, atherosclerosis and thrombogenesis.[52] Clinically, the harmful pro-oxidant effects predominate over the beneficial antioxidant effects, except in the central nervous system, where the beneficial antioxidant actions seem to prevail. Moreover, UA has important actions in the immune system and the development of some inflammatory processes with significant possible effects in various states of health and disease.

UA levels are an easily available and cheap marker of the risk of comorbidities associated with hyperuricemia, particularly CV disease. However, if UA is a true causal agent, an epiphenomenon, or if the increased levels of UA reflect an attempt to prevent or minimize oxidative damage, it cannot be answered on the basis of observational studies alone. Recent meta-analyses[35,36] indicate that hyperuricemia in itself could have a marginal effect as a CV risk factor, and that gout could be more determining factor in that risk. Even if that is the case, we should know from what UA acid values and/or gouty arthritis episodes or exposure time this risk appears. But above all, it should be demonstrated if its prevention reduces the risk. In any case, although limited, these findings support the advisability of aggressively treating the traditional CV risk factors in patients with gout.[35]

The same should be said for UA and its possible neuroprotective effects. The potential benefit of increasing the concentrations in patients with neurodegenerative diseases must be balanced with its possible adverse effects, which could include an increase in blood pressure, renal disease, coronary disease, stroke and a higher mortality, besides the known risks of gout and renal stones. The UA levels to achieve a neuroprotector effect are unknown, as well as if the potential benefit is clinically relevant. There is currently no clinical accepted recommendation to increase UA levels in any type of disease.

Ideally, to increase or decrease UA levels as part of the treatment of a disease should not increase the susceptibility of the patient to develop other diseases.[58] Since both high and low UA levels can be associated with various comorbidities, the modifying of its levels above or below certain values using drugs could give rise to undesirable secondary effects; therefore, attempt should be made to maintain its levels within the accepted normal range. In any event, the potential benefits of these therapeutic changes should be counterbalanced with the risk of increasing the incidence of other diseases.

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