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REVIEW ARTICLE

HYPERURICEMIA AS AN INTERDISCIPLINARY PROBLEM

HIPERURYKEMIA JAKO PROBLEM INTERDYSCYPLINARNY

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ABSTRACT

Introduction
Uric acid is the end product of purine nucleotide metabolism in the human body. Elevation of uric acid in the blood is known as hyperuricemia. Its participation in the development of gout is well known. According to the latest reports, it plays a role in developing cardiovascular and central nervous diseases.

Aim
This review article discusses the mechanisms and risk factors of hyperuricemia, its complications, and treatments that highlight hyperuricemia as a multi-faceted disorder requiring optimal treatment and rehabilitation.

Materials and methods
Pubmed and ClinicalKeys databases were used for searching for relevant research results. We focused on studies published in less than 5 years, but older references were also analyzed, if they brought valuable reports to our work.

Results
The analysis of the presented articles can indicate the role of hyperuricemia not only in the formation of gout, but also in hypertension, cardiovascular and kidney diseases and neurological disorders.

Conclusions
Due to the increase in the incidence of hyperuricemia worldwide and its consequences, maintaining an adequate level of uric acid is an essential aspect of patient management for clinicians. In addition to pharmacological treatment of hyperuricemia, patients should be considered for diet modification and increased physical activity. Further studies are needed to improve guidelines and recommendations for treating hyperuricemia and patient education.

Keywords: uric acid, gout, xanthine oxidase, physical effort

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STRESZCZENIE

Wstęp

Kwas moczowy stanowi końcowy produkt metabolizmu nukleotydów purynowych w organizmie człowieka. Hiperurykemią nazywamy stan za wysokiego poziomu kwasu moczowego we krwi. Powszechnie znany jest jego udział w rozwoju dny moczanowej oraz zgodnie z najnowszymi doniesieniami odgrywa on rolę w rozwoju chorób układu sercowo-naczyniowego oraz centralnego układu nerwowego.

Cel

W niniejszym artykule przeglądowym omówiono mechanizmy i czynniki ryzyka hiperurykemii, jej powikłania oraz metody leczenia, które podkreślają hiperurykemię jako wieloaspektowe zaburzenie wymagające optymalnego leczenia i rehabilitacji.

Materiał i metody

Do wyszukiwania odpowiednich wyników badań wykorzystano bazy danych Pubmed i ClinicalKeys. Skupiono się na badaniach opublikowanych w okresie krótszym niż 5 lat, ale przeanalizowano również starsze źródła, jeśli wnosiły wartościowe doniesienia do naszej pracy.

Wyniki

Analiza przedstawionych artykułów wskazuje, że hiperurykemia pełni rolę nie tylko w powstawaniu dny moczanowej, ale także może brać udział w patogenezie nadciśnienia tętniczego, miażdżycy, niewydolności serca, chorób nerek oraz zaburzeń neurologicznych.

Wnioski

Ze względu na wzrost częstości występowania hiperurykemii na całym świecie i jej konsekwencje, utrzymanie odpowiedniego poziomu kwasu moczowego jest dla klinicystów istotnym aspektem postępowania z pacjentem. Oprócz leczenia farmakologicznego hiperurykemii, należy rozważyć u pacjentów modyfikację diety i wzrost aktywności fizycznej. Potrzebne są dalsze badania w celu udoskonalania wytycznych i zaleceń dotyczących leczenia hiperurykemii a także poprawa działań w zakresie edukacji pacjentów.

Słowa kluczowe: kwas moczowy, dna moczanowa, oksydaza ksantynowa, wysiłek fizyczny

Introduction

Uric acid (UA) is the end product of purine metabolism. Under physiological conditions, UA synthesis and excretion are balanced in the body. Once this balance is disturbed, it leads to hyperuricemia (Yu and Cheng 2020; Zhu *et al.,* 2020). About 21% of people in the general population and 25% of hospitalized patients have asymptomatic hyperuricemia (George and Minter, 2022). According to epidemiological data, it is related to western habits characterized by a diet rich in meat and fructose and reduced physical activity (Cortese *et al.,* 2019). Elevated UA is an interdisciplinary problem as it affects the incidence of metabolic syndrome, hypertension, type 2 diabetes, acute renal failure, chronic kidney disease (CKD), ischemic heart disease, and heart failure (Sharaf El Din *et al.,* 2017; Chalès, 2019; Cortese *et al.,* 2019; Hisatome *et al.,* 2021). In addition, in recent years, the role of hyperuricemia in disorders of the neurological system and dementia has been growing. However, the most common manifestation in the body is gout (George and Minter, 2022), which manifests itself in recurrent bouts of arthritis (Cortese *et al.,* 2019).

It is uncertain whether hyperuricemia is a marker of risk for cardiovascular disease and kidney disease or an independent factor causing these conditions. However, appropriate UA management is undoubtedly essential in patient management.

Aim

This paper aims to present the evidence and mechanisms of hyperuricemia, related diseases, and methods of uric acid management.

Materials and methods

This review was created based on a systematic review of articles searched using the browser PubMed and Clinical Keys, applying keywords such as (hyperuricemia OR uric acid OR uric acid levels) AND (gout OR cardiovascular disease OR obesity OR renal disease OR neurological disorders OR treatment OR rehabilitation OR exercise). We focused on studies published in less than five years, but older references were also analyzed if they brought valuable reports to our work.

Results

Gout

The most common complication of hyperuricemia is gout, an inflammatory disease of the joints resulting from the deposition of sodium urate crystals. The disease can affect cartilage, bones, and tendons, but the most common location is the joints, especially the first metatarsophalangeal joint (Drabkin *et al.,* 2019). In most cases, hyperuricemia results from reduced excretion of UA in the kidneys, which may be associated with decreased kidney function, drug action, especially diuretics, and impaired renal UA transporters (Drabkin *et al.,* 2019). High blood UA levels can be caused by environmental and genetic factors (Voruganti *et al.,* 2013). So far, several genes have been described, such as SCL2A9, SCL22A12, or ABCG2, associated with an increased risk of hyperuricemia and gout (Reginato *et al.,* 2012; Voruganti *et al.,* 2013; Zhou *et al.,* 2014). More studies are examining the following genetic factors of hyperuricemia development. Tao *et al.* (2017) found an association between gout and single nucleotide polymorphism (SNP) of the P2X7R gene. The P2X7R receptor is an essential element of the ATP-P2X7R signaling pathway. Its polymorphisms play a significant role in the pathogenesis of gout by increasing the release of IL-1b. The relationship between the hypoxanthine phosphoribosyltransferase 1 (HPRT1) gene, encoding the HPRT – an enzyme involved in purine metabolism, with the pathogenesis of gout was known, among other things, in the form of Lesh-Nyhan syndrome. This syndrome is an inherited disease caused by complete HPRT deficiency characterized by neurological disorders and hyperuricemia. In recent years, more and more attention has been paid to partial HPRT deficiencies caused by missense mutations in the HPRT1 gene, which may be a potential cause of familial juvenile gout, with the simultaneous absence of neurological symptoms (Mishima *et al.,* 2020). Studies in mice show an association between elevated LDHD levels and elevated serum UA levels. The possible mechanism of this phenomenon may be the influence of the excess LDHD on the renal excretion of UA (Drabkin *et al.,* 2019). The nature of gout prompts the search for immunological causes of this condition. One of them is activating the innate immune response to sodium urate crystals. SNP in the toll-like receptor 4 (TLR4) gene encoding the TLR4 receptor is associated with an increased risk of developing gout. This receptor activates the NLRP3 inflammasome, which causes increased secretion of IL-1b, which is mainly responsible for the development of inflammation in response to sodium urate crystals (Qing *et al.,* 2013; Rasheed *et al.,* 2016). One of the latest reports is the suspicion that not only IL-1b but also the entire IL-1 family is involved in the pathogenesis of gout (Klück *et al.,* 2021). Increased release of IL-1a in response to sodium urate crystals has been observed, which may induce an increased release of other pro-inflammatory cytokines and the development of inflammation (Uratsuji *et al.,* 2012).

IL-18, although elevated in gout, does not significantly contribute to the development of joint inflammation but is associated with cardiovascular diseases, which may be the reason for the development of comorbidities in gout (Klück *et al.,* 2021). Recent studies have shown that the hormone leptin, secreted in large amounts by obese people, increases serum urate levels (Sharaf El Din *et al.,* 2017).

Cardiovascular and renal disease

Recent studies demonstrate that oxidative stress and inflammation have an influence on the basis of insulin resistance. Hyperuricemia can elevate oxidative stress in many cell lines. Hyperinsulinemia induced by insulin resistance enhances renal sodium reabsorption, which may lead to hypertension (Yu and Cheng, 2020). In addition, elevated levels of UA can lead to endothelial dysfunction through inflammation and oxidative stress, and the formation of an unstable lipid plaque in the coronary artery, ultimately leading to atherosclerosis (Yu and Cheng, 2020; Kimura *et al.,* 2021). Elevated levels of UA are common in patients with Heart Failure (HF). According to the New York Heart Association (NYHA) functional classification system and reduced exercise tolerance, there is also a connection between increased UA levels and increased HF symptoms (Borghi *et al.,* 2019).

The importance of hyperuricemia for the development of metabolic syndrome (MS) was determined in one prospective study, which evaluated 1.511 men and women aged 55–80 years who initially had no elements of this syndrome (Ragab *et al.,* 2017). Follow-up studies have shown a much higher incidence of many components of MS, namely hypertriglyceridemia, low HDL, and hypertension in people with hyperuricemia. The suggested mechanism is inhibition of endothelial nitric oxide (NO) synthase; in turn, NO reduction may underlie insulin resistance that leads to MS. It is assumed that hyperuricemia leading to hypertension, dyslipidemia, and atherosclerosis, contributes to the development of heart disease. Regardless of the above factors, it has been shown that hyperuricemia leads to the increased thickness of the intima-media complex on the carotid arteries and increased aortic stiffness in healthy subjects.

There is a relationship between UA retention and glomerular filtration rate (GFR) decline. Animal studies have shown that hyperuricemia causes the development of glomerular hypertension, leading to glomerular atherosclerosis and interstitial fibrosis (Ragab *et al.,* 2017). Moreover, it has been shown that an increase in UA levels correlates with increased albumin excretion in CKD. For every 1 mg / dL increase in UA, the risk of developing albuminuria increases by 80%. CKD is associated with an increased risk of impaired daily functioning or activity, regardless of age, gender, and other underlying conditions. An older person with GFR < 45 ml/min/1.73 m² has a three times higher risk of being unable to perform basic and complex everyday activities. Therefore, it is essential to propose and plan specific physical activities adapted to the patient's condition and natural abilities.

Neurological disorders

Due to the high heterogeneity in the studies so far, the different characteristics of the studied populations, and the methods of assessing cognitive dysfunctions, to assess the impact of hyperuricemia on the neurological system unequivocally.

UA has antioxidant properties and therefore has the potential to exert neuroprotective effects (Méndez-Hernández *et al.,* 2015). It has been found that gout may be associated with a lower risk of Parkinson's Disease (PD) due to the UA – alleviating oxidative stress mechanism (De Vera *et al.,* 2008). This hypothesis is confirmed by the studies by Engel *et al.* (2018) in which they stated that hyperuricemia or gout is inversely associated with dementia risk. It has been observed that serum uric acid levels are lower in elderly people with dementia without cardiovascular risk factors. This result supports the hypothesis that oxidative damage may play a role in the pathogenesis of dementia and

that uric acid may protect against cognitive impairment due to its antioxidant properties (Tuven *et al.,* 2017). A study conducted on the Chinese population proved that high levels of UA in the serum are associated with a lower incidence of mild cognitive impairment (Liu *et al.,* 2017). It is worth noting that this does not apply to people whose serum UA concentration is above the norm.

On the other hand, in the Netherlands, the relationship between the level of UA in the blood serum and brain atrophy and the incidence of cognitive disorders was investigated (Verhaaren *et al.,* 2013). It has been found that hyperuricemia affects the volume of the brain, mainly white matter, and primarily lowers the speed of information processing. It is essential that it was also possible to show that people with normouricemia did not have such problems. Surprisingly, the decrease in white matter volume was associated with an increase in gray matter volume. However, it was found not to be related to hyperuricemia, and most likely, the reason is that atrophic white matter may give a similar signal in imaging to gray matter.

Han *et al.* (2017) published a study that revealed several risk loci for neurodegenerative diseases associated with hyperuricemia. They combined the Montreal Cognitive Assessment scale (MoCA) and Mini-Mental State Examination (MMSE) with the genome-wide association study (GWAS). The study showed a significant association of the seven associations of one nucleotide polymorphisms with the MoCA assay at the genome-wide significance level. The most significant relationship was observed in the KTN1 gene, which encodes the kinectin protein. It is found mainly in the endoplasmic reticulum in the dendrites and the body of the nerve cell and plays a key role in regulating the shape, spread, and migration of neuronal cells (Toyoshima and Sheetz, 1996).

Uremia may be associated with numerous neuromuscular complications. The most common is uremic neuropathy. It is predominantly a sensory polyneuropathy caused by axonal degeneration with secondary demyelination. The symptoms of uremic polyneuropathy include dysesthesias, muscle cramps, and restless legs (Al-Hayk and Bertorini, 2007). Neuropathy occurs in a minimum of 65% of patients who are about to begin dialysis for CKD. The pathophysiologic basis of uremic neuropathy is suggested to be due to the retention of neurotoxic molecules in the middle molecular range, chronic hyperkalemic depolarization of nerve fibers, and prolonged nerve conduction velocities induced by high parathyroid hormone (Basturk *et al.,* 2017).

Discussion

Hyperuricemia and gout are associated with increased death risk and decreased free-walking ability, so it is essential to implement the appropriate therapy (Liu *et al.,* 2022). The group of drugs considered first-line drugs is xanthine oxidase inhibitors, which inhibit the formation of UA and thus reduce its concentration in the serum (Figure 1). This group includes allopurinol as a first-line drug and febuxostat as an alternative choice (FitzGerald *et al.,* 2020).

An important advantage of xanthine oxidase inhibitors is their lack of negative influence on kidney function. Therefore they can be used in people with chronic renal failure (Peng *et al.,* 2020). Allopurinol is selected as a first-line drug, as indications emerged in 2018 about a higher risk of death from cardiovascular complications of febuxostat (William B. White *et al.,* 2018). However, more recent studies do not support these results and do not show a greater cardiovascular risk in people treated with febuxostat compared to allopurinol (Al-Abdouh *et al.,* 2020; Mackenzie *et al.,* 2020), and even more effective in lowering blood UA levels in people with chronic kidney disease (Peng *et al.,* 2020). The results of other studies (Ziga-Smajic *et al.,* 2020) also indicate a stronger effect of febuxostat on lowering the serum UA concentration compared to allopurinol. An important factor is the lower cost of allopurinol therapy and, thus greater availability

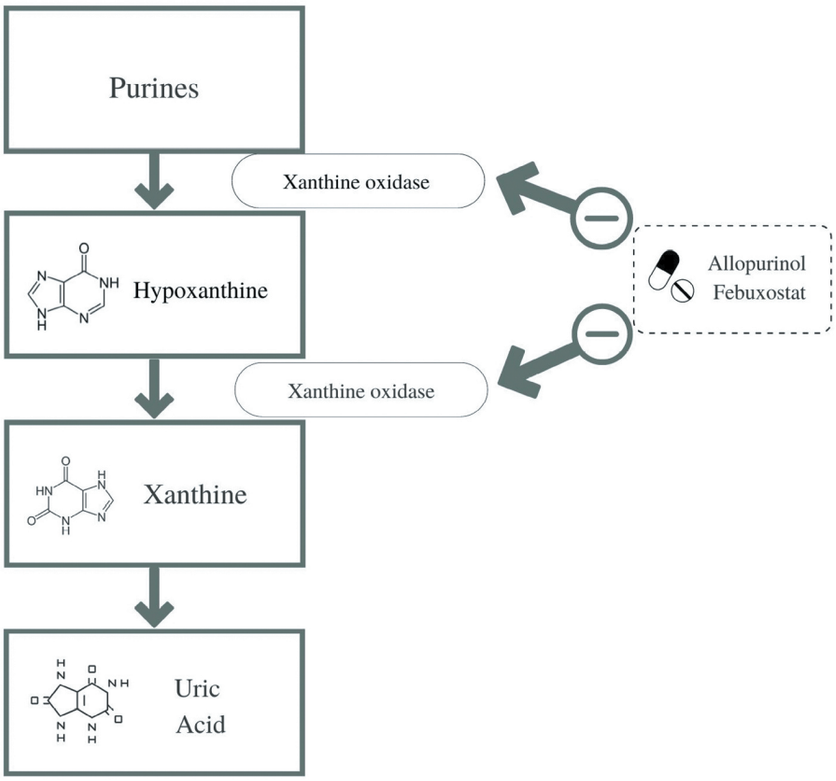

Figure 1. Pharmacological urate-lowering therapy – xanthine oxidase inhibitors

for patients. Alternative drugs that lower UA levels are probenecid and pegloticase, which are not recommended as drugs of first choice (FitzGerald *et al.*, 2020). Despite the effectiveness of these drugs in reducing UA levels, the American College of Rheumatology (ACR) recommends pharmacological urea-lowering therapy (ULT) for patients with symptomatic gout but not for patients with asymptomatic hyperuricemia (FitzGerald *et al.*, 2020). This is because no evidence controlling UA levels protects patients from developing gout. However, it is worth remembering that gout is not the only consequence of hyperuricemia, and the control of UA concentration through the use of allopurinol has been proven to reduce the development of arterial hypertension and increase the thickness of the carotid inner membrane (Liu *et al.*, 2015). In addition to pharmacotherapy, attention should be paid to the crucial role of lifestyle changes, including dietary modification and increased physical activity (Figure 2).

A diet rich in red and processed meat, sugar, and refined grains, typical for Western countries, is associated with the development of hyperuricemia, which is associated with a 42% higher risk of developing gout (Vedder *et al.*, 2019). Alcohol (especially beer), seafood, and fruit juices should also be avoided because a purine-rich diet is associated with a five-fold higher risk of recurring bouts of the disease. Meals should be eaten regularly (3–4 times a day), and starvation is contraindicated. A minimum of 2 liters of fluids a day should be drunk (Pęksa and Malinowska-Karpiel, 2019). Consuming large amounts of tea and limiting fluid intake is common in the elderly, contributing to hyperuricemia (Winder and Chudek, 2020). Patients with gout do not need to be concerned about limiting their daily take of coffee. There is growing evidence proving that caffeine reduces the risk of gout by inhibiting xanthine oxidase, which results in increased renal blood flow and improved urate excretion via the urinary

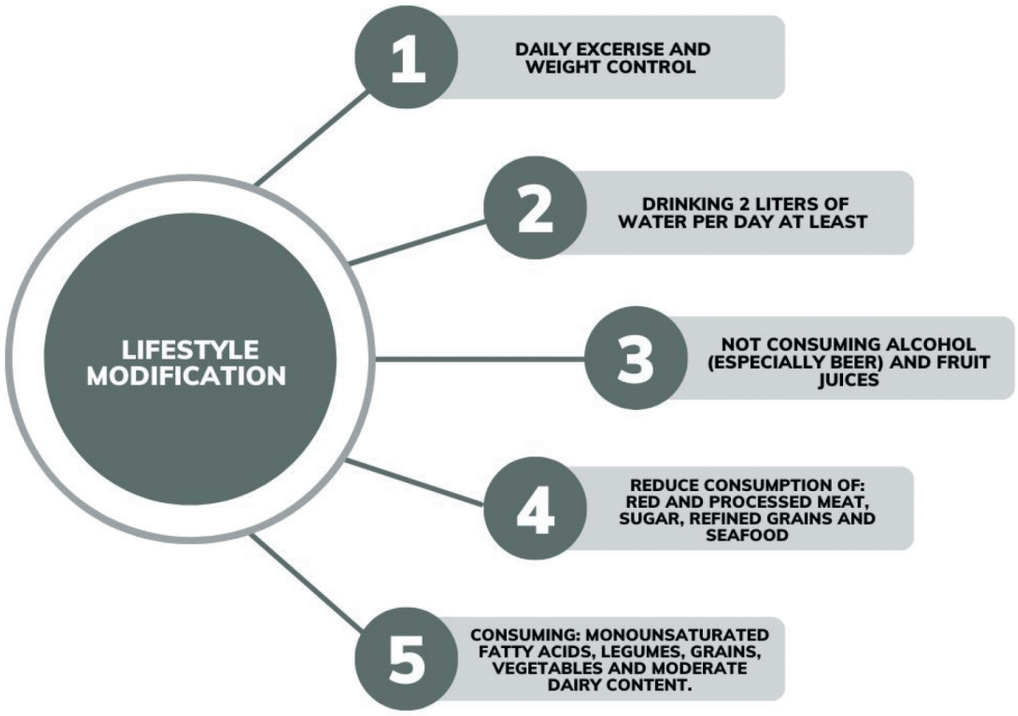

Figure 2. Lifestyle modification and strategies to reduce hyperuricemia

tract (Sautner *et al.*, 2022). It should be noted that the caffeine effect is just supporting the reduction of uric acid and is not an effective treatment tool. However, in the case of the Mediterranean diet, which is rich in monounsaturated fatty acids, legumes, grains, fruit and vegetables, moderate alcohol and dairy content, and low meat content, a significant decrease in UA concentration was observed in both women and men. Additionally, no gout attacks occurred during the study. It has also been confirmed that skimmed milk powder (SMP) enriched with glycomacropeptide (GMP) and G600, standard SMP, and lactose powder can alleviate gout symptoms and reduce the frequency of exacerbations within three months (Li *et al.*, 2018). Evidence has demonstrated a beneficial effect of weight loss in gout-overweight patients in reducing UA levels and gout attacks (Vedder *et al.*, 2019). Nielsen *et al.* (2017) conclude that a loss of more than 7 kg and/or more than 2 kg per week by surgery or diet has a beneficial effect on plasma UA levels in the medium to long term. That weight loss more than 3.5 kg has shown a beneficial effect on the incidence of gout attacks in the medium/long-term follow-up. Gout can develop as intermittent episodes of acute arthritis or as subcutaneous nodules. Due to the pain and deformities of the feet, one of the elements of rehabilitation is the selection of appropriate footwear. Gout patients report such problems as the inability to wear shoes during exacerbations of pain, uncertainty about the type, design, and choice of shoes, and difficulties in finding shoes due to the presence of subcutaneous nodules on the feet (Frecklington *et al.*, 2019). The various features of the footwear help to reduce the burden of foot pain and disability in people with gout. In selecting footwear that will allow such patients to engage in physical activity, the key is a good fit, cushioning, lightness, and sufficient space for the foot to be considered important factors affecting the comfort of using the footwear. It should be remembered that in some patients, the choice of footwear will be limited due to a poor financial situation or a profession requiring a good appearance. Another key

element in gout rehabilitation is exercise. It was suggested that physical activity was independently associated with decreased serum UA levels and the prevalence of hyperuricemia. In contrast, sitting time was independently associated with increased serum UA levels and the prevalence of hyperuricemia (Dong *et al.,* 2021). Park *et al.* (2019) found that people who spent more than 10 hours per day in sedentary behavior were more likely to have hyperuricemia than those who spent less than 5 hours per day in sedentary behavior. So they considered that participation in regular physical activity and reduced sedentary time is highly recommended to reduce the prevalence of hyperuricemia. Goh *et al.* (2019) showed that aerobic and mind-body exercise appears to be the two most effective forms of rehabilitation therapy for pain and function, bearing in mind that strengthening and stretching exercises appear to be good for moderate performance improvement. However, the results of other studies have shown that during very long but not very intense exercise, there were no changes in the excretion of uric acid, although significant changes in the excretion of electrolytes were found (Wołyniec *et al.,*2018). Fundamental in the elderly are mind-body exercises, such as tai chi and yoga, characterized by low to moderate intensity. A key element of rehabilitation with their use is an exercise with inhalation control and slow, controlled movement. Refraining from rehabilitation and additional physical activities during gout flares is strongly recommended. For patients in severe pain during a gout flare, using assistive devices to move, like wheelchairs and crutches, is advised (Stewart *et al.,* 2020). Treatment of uremic neuropathy relies on hemodialysis, which appears to be effective in retarding the progression of established uraemic neuropathy and renal transplantation, which seems to be most crucial for patients (Smyth *et al.,* 2019). Individualized exercise during maintenance hemodialysis significantly improved the exercise capacity and health-related quality of life (HRQoL) for uraemic patients within a short period. It could therefore be used as a simple, cost-effective therapeutic approach (Wu *et al.,* 2014).

Conclusions

Hyperuricemia leads not only to gout but also to cardiovascular diseases, kidney diseases and neurological disorders. Hence it should be perceived as an interdisciplinary problem. These disorders are related to oxidative stress induced by UA and genetic and immunological stress through the interleukin IL-1b pathway.

Due to the increase in the prevalence of hyperuricemia worldwide and its consequences, maintaining adequate UA levels is becoming an important aspect of patient management for doctors. We should focus on urate-lowering drugs, nutritional education, bodyweight control, and exercise. Future research may need to evaluate which hyperuricemia treatment strategies should be chosen first for patients.

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