Cerrahpaşa Med J 2024; 48(2): 191-196 REVIEW

High Fructose Consumption and Metabolic Syndrome from Gout Perspective

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Cite this article as: Aydın Ü, Kozanoğlu E, Tuli A. High fructose consumption and metabolic syndrome from gout perspective. *Cerrahpaşa Med J.* 2024;48(2):191-196.

Abstract

Uric acid is formed as a consequence of the catabolism of purine nucleotides. The removal of uric acid from the body is mainly carried out by the kidneys via urine and, to a lesser extent, by the intestinal tract via feces. Excretion and reabsorption of uric acid from the intestinal tract, and especially from the kidneys, are carried out by special transporters. Genetic variations in these carriers have been related to increased or decreased serum uric acid levels. Uric acid synthesis increases for various reasons that increase the destruction of purine nucleotides, causing serum uric acid levels to rise. Although hyperuricemia, with a mean serum uric acid level above 6.8 mg/dL, does not always cause gout, if hyperuricemia is not kept under control, it can result in gout; an inflammatory disease characterized by the crystallization of monosodium urate. As well as non-modifiable factors such as age and ethnicity; diet, which is one of the modifiable factors, can promote gout or recurrence of gout flare-ups. Excessive consumption of products with high fructose content can cause hyperuricemia and gout. In addition, the increase in uric acid resulting from excessive consumption of fructose, and overall and sustained high serum uric acid levels have been shown to cause various disorders that will give rise to metabolic syndrome. In this review, the interwoven relationships between hyperuricemia—an increase in serum uric acid levels—and the resulting gout, as well as metabolic syndrome, and the role excessive fructose consumption plays in these, have been investigated.

Keywords: Uric acid, hyperuricemia, gout, fructose, metabolic syndrome

Introduction

Uric acid—whose form at physiological pH also named urate—is the excretion product of endogenous and exogenous purine nucleotides. Guanine and hypoxanthine are transformed into xanthine in the liver by the catalysis of guanine deaminase and xanthine oxidase enzymes, respectively. The xanthine is then converted into uric acid by xanthine oxidase. Higher primates excrete purine nucleotides as uric acid, 70% of which is excreted in the urine, due to the absence of the enzyme uricase, which is found in other mammals and converts uric acid into the more water-soluble allantoin.[1,2] Of the uric acid, which is produced primarily in the liver, intestines, and other tissues such as muscle, 1/3 is excreted from the body through the gastrointestinal tract and 2/3 through the kidneys. About 9% of uric acid is reabsorbed from the proximal tubule after filtration through the glomeruli in the kidneys. This reabsorption has been shown to be carried out by some specific carriers.[3] These transporters (shown in Figure 1) include urate transporter 1 (URAT1), organic anion transporter 1, 3, and 4 (OAT 1, 3, and 4), ATP-binding cassette superfamily G member 2 (ABCG2), sodium-phosphate transporter 1 and 4 (NPT1 , and 4), multidrug resistance protein 2 and 4MRP 2, 4 (MRP 2, and 4), and glucose transporter 9GLUT 9 (GLUT 9glucose transporter 9).[4] Urate transporter 1 is a transporter that has a major role in the reabsorption of uric acid from the apical membrane, and its deficiency is characterized by hypouricemia. URAT1 performs the reabsorption by expelling a monovalent anion from the cell. OAT4, on the other hand, provides urate reabsorption by acting as a urate/anion exchanger, which is 52% identical to URAT1 and has less affinity for urate.[4-6] NPT1 is a sodium-dependent phosphate cotransporter, while NPT4 is a voltage-dependent sodium phosphate transporter. Both are responsible for the secretion of urate from the apical membrane, and many single-nucleotide polymorphisms (SNPs) of these transporters have been related to hyperuricemia and gout.[7,8] MRP2 and MRP4 are transporters that carry p-aminohippurate and organic anions in renal proximal tubular cells and are responsible for the ATP-dependent transport of urate from the cell to the lumen, and their SNPs have been reported to be associated with hyperuricemia.[4,7,9] Besides, OAT1 and OAT3, located in the basolateral membrane, assist the uptake of uric acid into intracellular tubular cells and have a significant role in urate excretion as urate/α-ketoglutarate exchangers.[10,11] Interestingly, before the urate transport function of GLUT9 was revealed by genetic studies, it was thought to be merely a glucose transporter. Genome-wide association studies (GWAS) have shown that SNPs of the GLUT9 also have a bearing on gout. In addition, the loss of function of this transporter causes renal hypouricemia.[12,13] ABCG2—a transporter that is thought to be associated with early gout—is highly expressed in the intestines, and allows extra-renal uric acid excretion by ATP hydrolysis.[4-6] In line with this information, it can be stated that the balance between uric acid production and excretion determines serum uric acid levels. This balance is disturbed by various factors such as alcohol consumption, excessive fructose intake, and a purine-rich diet, which will all increase production.[3]

Received: January 3, 2024 **Revision Requested:** February 27, 2024
Last Revision Received: April 27, 2024 **Accepted:** May 16, 2024
Publication Date: July 17, 2024
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DOI: 10.5152/cjm.2024.24001

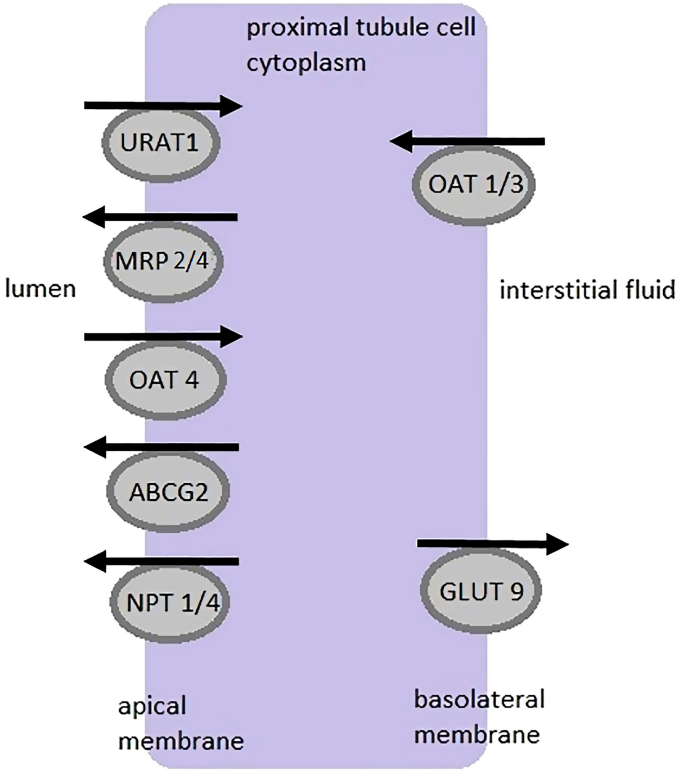

Figure 1. Urate transporters in kidney proximal tubule cells. The direction of the arrows shows the transport way of uric acid. Uric acid is reabsorbed by URAT1 (urate transporter 1) and OAT4 (organic anion transporter 4), while ABCG2 (ATP-binding cassette superfamily G member 2), MRP2/4 (multi-drug resistance protein 2/4), and NPT1/4 (sodium-phosphate transporter 1/4) secrete uric acid into the lumen. OAT1 (organic anion transporter 1) and OAT3 (organic anion transporter 3) uptake uric acid into the proximal tubule cell, while GLUT 9 (glucose transporter 9) takes part in the exit of uric acid from the cell.

Fructose is the only carbohydrate that causes uric acid production during its metabolism. When fructose is taken into the body, it passes from the lumen into the enterocytes via glucose transporter-5(GLUT5). Fructose, absorbed independently of insulin, enters the metabolic process that will be discussed in detail in later sections. Fructose is first phosphorylated by fructokinase, and ATP is rapidly consumed. This leads to a decrease in intracellular phosphate levels, degradation of ADP by AMP deaminase, and ultimately to the production of IMP and uric acid (Figure 2). In addition, the insulin level, which rises with fructose intake, increases urate reuptake and reduces its excretion from the kidneys, causing serum uric acid levels to rise.[14,15]

Hyperuricemia, which refers to elevated serum uric levels, can be associated with some diseases, such as hyperinsulinemia, type 2 diabetes, obesity, hypertension, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, and cardiovascular diseases.[3]

Hyperuricemia has recently been suggested as one of the new components of metabolic syndrome. It is also supposed that a holistic approach is needed to understand the mechanisms of fructose metabolism, hyperuricemia, and gout disease. In the current article, the relationship between gout disease and fructose metabolism with regards to the occurrence of metabolic syndrome—a growing health problem in the community—is reviewed, and information is provided about hyperuricemia and gout, the relationship between fructose metabolism and gout, and the roles these factors play in the development of metabolic syndrome. Although there are articles and/or reviews that evaluate the mentioned topics separately, we believe this review, which examines the relationship between uric acid and fructose metabolism, hyperuricemia, and gout, and their relationship with metabolic syndrome, readdresses this important and current issue through the lens of new information in a holistic manner, thus contributing to our common scientific knowledge.

Hyperuricemia and Gout

Hyperuricemia refers to a rise in serum urate levels above 6.8 mg/dL. Many researchers typically accept this value, although there are different cutoff values for men and women. Exceeding this limit value in serum urate levels does not indicate that symptoms of hyperuricemia or gout will develop. The asymptomatic state of hyperuricemia is due to the fact that monosodium urate (MSU), the characteristic feature of gout, has not yet crystallized and settled in the joints. However, hyperuricemia may pose a risk for the development of some diseases such as hypertension or cardiovascular diseases. Gout is an acute or chronic inflammatory

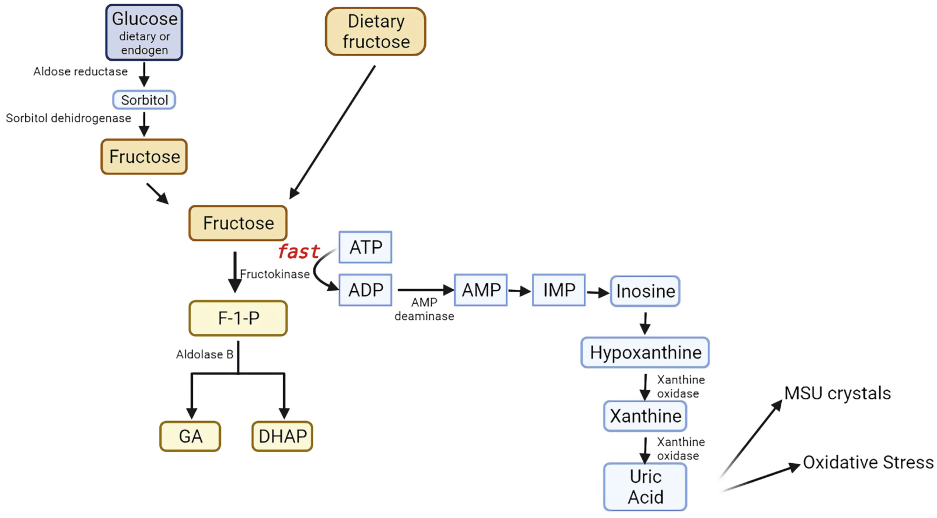

Figure 2. Uric acid production from fructose metabolism (F-1-P, fructose-1-phosphate; GA, glyceraldehyde; DHAP, dihydroxyacetone phosphate).

disease with tissue damage caused by the precipitation of crystalized MSU in the joints, kidneys, or subcutaneous regions.[16-18] Approximately 25% of hyperuricemia patients have deposition of MSU crystals, especially in the metatarsophalangeal joint. The clinical manifestation of gout occurs with acute inflammatory arthritis of the lower extremity joints, which is called gout flare, and is characterized by pain that usually lasts less than 12 hours. Uncontrolled and persistently high levels of hyperuricemia can lead to recurrences of gout flares, prolongation of flares, development of tophus, and chronic gouty arthritis. Gout flares occur by triggering the innate immune system through MSU crystals affecting monocytes and macrophages. MSU-induced gout inflammation occurs via the functions of these cells, the participation of NLRP3 (the nucleotide-binding oligomerization domain (NOD-), leucine-rich-repeat domain (LRR-) and pyrin domain-containing protein 3) inflammasome, anti-inflammatory cytokines (e.g. TNF-alpha, IL-10, IL-37) and proinflammatory cytokines (e.g. IL-1β, IL-8, IL-17). However, MSU crystals alone do not constitute a sufficient signal for an immune response. The first signals that trigger inflammation may come from fatty acids due to alcohol consumption or a large meal, or NLRP3 activation from reactive oxygen species (ROS) production, which will be discussed later. This may explain why gout flares do not always occur despite the presence of MSU crystals.[18-20]

Population surveys in Asia, Europe, and North America have revealed that the prevalence of gout in adults is between 0.68% and 3.9%.[19] The highest prevalence of gout occurs in Oceania, followed by North America. A higher prevalence is shown in developed countries than in developing countries.[20]

Risk Factors for Gout Development

There are non-modifiable risk factors for gout development, including gender, age, and race or ethnicity. In addition, due to the previously mentioned GWAS, genetic differences in urate carriers constitute important risk factors for gout. The development of gout is much higher in men than in women, although the stark difference in this proportion decreases during the menopausal period of women over 65 years of age. In addition, from an ethnic point of view, African Americans have a higher prevalence of gout than Caucasians, which is attributed to a higher incidence of hypertension in African Americans. It is noteworthy that the prevalence of gout is higher in the Maori population in New Zealand compared to Europeans. This high prevalence of hyperuricemia and gout in the Maori population is associated with comorbidities of obesity, hypertension, and diabetes resulting from genetic predispositions triggered by alcohol- and purine-rich diets.[21] At this point, in addition to genetic predisposition, it is necessary to emphasize the risk factors that can be regulated, such as diet and lifestyle.[22] Alcohol, fructose-sweetened foods and beverages, and purine-rich foods are dietary factors that cause an increase in uric acid levels. Alcohol consumption raises uric acid levels because it triggers the formation of more uric acid as a result of purine catabolism by triggering ATP breakdown. Additionally, consuming alcoholic beverages containing purines, such as beer, increases serum lactate levels, which inhibits renal uric acid excretion. Besides, it is stated that there are differences between the effects of various alcohol types on the increase in uric acid levels. For example, increased consumption of beer and liquor leads to an increase in uric acid levels, while increased wine consumption does not have this effect. Nevertheless, all types of alcohol are associated with recurrences of gout attacks. Foods such as meat, organ meat, and seafood cause an increase in uric acid production since they are high in purines. It is emphasized that consuming these foods above normal levels increases the risk of gout development and recurrence of gout attacks; therefore, their consumption should be limited by gout patients. Increasing daily meat consumption by one serving and additional weekly consumption of seafood increases the risk of gout by 21% and 7%, respectively. However, it has been noted that purine-rich vegetables did not raise the risk of gout, and it was thought to be related to a decrease in purine absorption due to the fiber content in vegetables.[21,23,24] Zhang et al.[25]examined gout patients for 1 year to determine the relationship between the intake of purine-rich foods and gout attacks. According to the data they obtained, they suggested that consumption of purine-rich food increases gout attacks by about 5 times, and thus, it is recommended to avoid or limit the intake of animal foods containing purines.

Fructose Consumption and Gout

Fructose occurs naturally in fruits and vegetables in the form of a monosaccharide and as sucrose, a disaccharide that is the condensation product of fructose and glucose in equal ratio. Fructose, often as high-fructose corn syrup and sucrose, is widely used as a food sweetener in soft drinks and many foods.[26-28] These sugar-added foods and beverages, whose consumption is increasing in underdeveloped countries while decreasing in Western Europe, Australia, and North America,[29] are determined to be the main source of fructose consumption ,and it is stated that they provide 15%-17% of daily energy intake.[28] Although fruits are very rich in fructose content, the effect of fruit consumption on the development of gout is more complex. The intake of not only fructose but also other molecules such as flavonoids and vitamin C, which lower serum uric acid levels, or fiber, which reduces fructose absorption, necessitates further investigation of fruit consumption in terms of gout risk.[30]

Fructose Metabolism

Fructose taken with food is absorbed by GLUT5 on the apical border of small intestinal cells and is delivered to the systemic circulation via GLUT2 in the basolateral part. Liver cells, where most of the metabolism is carried out, take in the fructose that has entered the systemic circulation using GLUT2 and GLUT8 to metabolize it. GLUT5 is a transporter inducible by the presence of fructose, and its expression is also regulated by carbohydra te-responsive element-binding protein (ChREBP). The increase in GLUT5 due to the high amount of fructose enhances the absorption of fructose in the enterocytes, and thus the fructose concentration that passes into the portal vein also rises. Fructose taken into the cell by GLUT5 is phosphorylated by fructokinase, which has no feedback inhibition in enterocytes. Excessive fructose intake not only increases the expression of GLUT5, which is involved in the regulation of fructose metabolism in enterocytes but also causes the enterocyte's capacity to be exceeded in order to metabolize fructose.[26,27,29]

In addition, fructose produced endogenously—via the sorbitol pathway after glucose intake—is metabolized in the liver. High blood glucose, high salt diet, oxidative stress (ROS production), fructose, and uric acid cause stimulation of aldose reductase, and thus sorbitol is produced. Fructose is then produced from sorbitol by sorbitol dehydrogenase and enters the metabolic process (discussed below) in the liver.[31,32]

Fructose is converted into fructose-1-phosphate by hepatic ketohexokinase (also named fructokinase) in the liver. Fructose-1-phosphate is divided into dihydroxyacetone phosphate (DHAP) and glyceraldehyde by aldolase b (Figure 2). In this metabolic process, the hormonal control and the phosphofructokinase

regulation step in glycolysis are bypassed. The DHAP and glyceraldehyde can be transformed into glucose by gluconeogenesis, converted into lactate and released into circulation, or converted into glycerol-3-phosphate and acetyl-CoA, which enter lipogenesis.[26-28] The fact that fructokinase is not controlled by its product with negative feedback causes the continuous conversion of fructose to fructose-1-phosphate using ATP (which produces ADP). This causes a rapid decrease in the level of phosphate within the cell. In response to this, AMP deaminase is stimulated, thus inositol phosphate (IMP) is produced from AMP. While uric acid is produced as a by-product of fructose metabolism as a result of purine degradation with ongoing reactions of IMP, the level of intracellular phosphate is increased with the inorganic phosphate released.[27] It is also stated that high fructose consumption causes an increase in serum uric acid levels by decreasing renal[33] and intestinal[34] uric acid excretion.

In a systematic review and meta-analysis conducted by Wang et al. in 2012,[35] it was investigated how uric acid levels were affected by diets in which fructose was isocalorically replaced with other carbohydrates or under hypercaloric and isocaloric conditions in which a control diet was supplemented with more energy from fructose. As a result, it was concluded that the substitution of isocaloric fructose instead of other carbohydrates did not cause a significant increase in serum uric acid levels, but the intake of hypercaloric fructose increased serum uric acid levels in a way that could cause hyperuricemia. Bruun et al.,[36] in their study by including sucrose-containing beverages in which fructose is the major component, found that daily intake of 1 L of sucrose-sweetened beverages for 6 months increased circulating uric acid levels by ~15% (P = .02) compared to isocaloric milk, diet cola, and water. Another systematic review and meta-analysis[37] examined the association of fructose consumption with gout and hyperuricemia. Accordingly, the data showed that high fructose consumption was associated with the risk of gout with a risk ratio of 1.62, 95% CI of 1.28-2.03, P < .0001. Meneses-León et al.[38] stated in their study examining the effect of sugar-sweetened beverages on the risk of hyperuricemia in Mexican adults that uric acid was higher (P < .001) in participants with ≥7 servings/week sugar-sweetened beverages intake than in those with <1 serving/week intake. In addition, when they examined the consumption of portions from the lowest category to the highest category, it indicated that the participants experienced a 2.6 increase in the probability of hyperuricemia. Accordingly, the odds of hyperuricemia were increased by 44% in the 2-6 servings/week group (OR = 1.44; 95% CI: 1.13, 1.84) and by 89% in the ≥7 servings/week category, compared to the <1 servings/week category (OR = 1.89; 95% CI: 1.39, 2.57). However, another meta-analysis of studies conducted up to 2017 to examine the association of sugar-sweetened soft drinks and fructose consumption with gout and hyperuricemia suggests that sugar-sweetened soft drink consumption increases the risk of gout and hyperuricemia. Nonetheless, according to this study, more studies are needed for a meta-analysis of the effects of fructose consumption.[39] The data are summarized in Table 1.

Relationships Between Hyperuricemia, Gout, Fructose Consumption, and Metabolic Syndrome

Metabolic syndrome is a condition related to type 2 diabetes, hypertension, dyslipidemia, and abdominal obesity. Cardiovascular diseases and NAFLD are also associated with metabolic syndrome. It is stated that the prevalence of gout and metabolic syndrome increases in parallel with each other.[40] Many clinical studies have shown a higher prevalence of metabolic syndrome in gout patients compared to the general population.[41,42] According to the United States of America Third National Health and Nutrition Examination Survey (NHANES-III) data, the prevalence of metabolic syndrome in individuals with gout is 63%, and also these individuals with gout are 3 times more likely to develop metabolic syndrome than patients of the same age without gout.[20] Schlesinger et al.,[43] in their study examining the metabolic syndrome severity score in gout patients, concluded that medium to high metabolic syndrome severity was significantly common in gout patients (47.33% vs. 21.16% no gout; P value <.0001).

Dyslipidemia, obesity, chronic renal disease, diabetes, and hypertension (together known as metabolic syndrome as mentioned above), are common in hyperuricemia and/or gout patients, all of which are known risk factors for cardiovascular diseases.[44] In the article of Choi et al., it is shown that the prevalence rates of all individual metabolic abnormalities (abdominal obesity, hypertriglyceridemia, low HDL cholesterol, fasting glucose ≥110 mg/dL or medication use, high blood pressure or medication use) were

Table 1. Summarized Data

Investigation	Conclusion	References
Effects of fructose intake on serum uric acid in controlled dietary trials	The use of isocaloric fructose does not cause an increase in serum uric acid levels. Hypercaloric fructose intake increases serum uric acid levels, causing hyperuricemia.	35, 36
Consumption of sugar sweetened beverages and dietary fructose in relation to risk of gout and hyperuricemia	High fructose consumption is associated with hyperuricemia and gout risk.	36-38
Interconnections between gout and metabolic syndrome	The incidence of metabolic syndrome increases in gout patients. Individuals with gout are 3 times more likely to develop metabolic syndrome than patients of the same age without gout.	20, 40, 41, 43
Novel gout-associated comorbidities related to metabolic syndrome	Metabolic abnormalities (abdominal obesity, hypertriglyceridemia, low HDL cholesterol, fasting glucose ≥110 mg/dL, high blood) were significantly higher in patients with gout than in those without gout. It has been determined that gout patients have a risk of developing type 2 diabetes. Hypertension is directly related to a high serum uric acid level, and the incidence of coronary heart disease in gout patients is given as 25%. Hyperlipidemia is in the range of 25%-60% in gout patients. Hyperuricemia may play a role in promoting inflammation, hypertension and cardiovascular disease, adipogenesis and lipogenesis, insulin and glucose dysregulation, and liver disease.	23, 38, 42, 44

significantly higher in patients with gout than in those without gout.[42] While the rate of hyperuricemia in overweight individuals is 11.4%, it is stated that hyperlipidemia is in the range of 25%-60% in gout patients. The observed relative risk for type 2 diabetes mellitus in patients with gout was 1.34 (95% CI 1.09-1.64). On the other hand, hypertension is directly associated with high serum uric acid levels, and according to 2010 data, the prevalence of coronary heart disease in gout patients in the United States is given as 25%.[23] The data are summarized in Table 1.

High serum uric acid levels cause an increase in blood pressure by disrupting endothelial function by activating the renin–angiotensin system and reducing nitric oxide bioavailability. Additionally, they increase intracellular oxidative stress by activating NADPH oxidase. While increased mitochondrial oxidative stress inhibits aconitase in the tricarboxylic acid cycle, causing citrate accumulation, triggering lipogenesis, and impairing fatty acid oxidation. This also results in impairing glucose delivery and GLUT4 translocation, causing insulin resistance.[45,46] Moreover, in vitro studies on HepG2 cells have shown that hyperuricemia-induced oxidative stress impairs the insulin response by phosphorylating insulin receptor substrate 1 (IRS-1) and protein kinase B (also named Akt). Akt stimulates both the storage of glucose as glycogen and the lipid synthesis from excess glucose while inhibiting glycogen breakdown and de novo glucose synthesis in the liver.

Inhibition of AMP-activated protein kinase by uric acid induces gluconeogenesis and hepatic lipogenesis. Inflammatory signals developed by uric acid-derived ROS in parenchymal and non-parenchymal liver cells cause over-expression of acetyl-CoA carboxylase 1, fatty acid synthase, and stearoyl-CoA desaturase 1, leading to lipid accumulation.[3,27,40,45,46] In addition to all these, as explained in the previous section, fructose has been suggested to cause metabolic syndrome because it causes uric acid formation.[46] Uric acid triggers the lipogenic effect of fructose by causing an increase in the expression of the fructokinase enzyme through the activation of ChREBP in the liver. The oxidative stress caused by the depletion of ATP resulting from the phosphorylation of fructose by fructokinase, and the activation of NADPH oxidase by the formed uric acid, emerge as the basic processes through which fructose causes lipid accumulation. Mice deficient in fructokinase are protected from the development of metabolic syndrome despite a high fructose diet. In addition, adipocytes can produce uric acid by virtue of having purine catabolism enzymes. Visceral adipose tissue is associated with hyperuricemia, and obesity has been reported to enhance the activity and expression of the xanthine oxidase enzyme. Oxidative stress caused by increased NADPH oxidase activity and by ROS induced via uric acid produced in adipose tissue is the cause of obesity-induced inflammation and metabolic syndrome.[47,48]

Conclusion

Hyperuricemia occurs when uric acid synthesis increases or its excretion decreases. Gout, which occurs as a result of the persistence of hyperuricemia, can be associated with excessive fructose consumption and metabolic syndrome. ATP depletion, which occurs during the metabolism of excess fructose in the liver, results in the production of uric acid and also causes oxidative stress. Uric acid can cause hypertension by activating the renin–angiotensin system, insulin resistance by impairing insulin response, and NAFLD and metabolic syndrome by triggering lipogenesis due to excessive fructose consumption. As a result, it can be concluded that individuals with hyperuricemia should avoid excessive fructose consumption in order to not to aggravate the risk of gout, to abstain from the recurrence of gout attacks, and to avoid the risk of metabolic syndrome.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Ü.F.A., E.K.; Design – Ü.F.A.; Supervision – E.K., A.T.; Resource – Ü.F.A., E.K.; Data Collection and/or Processing – Ü.F.A.; Literature Search – Ü.F.A.; Writing – Ü.F.A.; Critical Review – E.K., A.T.

Acknowledgment: We would like to thank Erkan Aydın, Research Assistant at Ağrı University Translation and Interpreting Studies Department, for proofreading the article's English version.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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