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The Effects of High Dietary Fructose Consumption on the Development of Gout

Brief Review

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Michael E Anderson, and Orien L Tulp*

Colleges of Medicine and Graduate studies, University of Science Arts and Technology, Montserrat, British West Indies

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***Corresponding author:** Orien L Tulp, PhD, MD, FACN, CNS, Professor, Colleges of Medicine and Graduate Studies, University of Science Arts and Technology, Montserrat, MSR1110, British West Indies, and the Einstein Medical Institute, North Palm Beach, FL 33409, USA.

Abstract

Fructose is frequently used as a food ingredient due to its low production costs, its significant sweetening power and its easy incorporation into a broad variety of foods and beverages. In recent years, it has been observed that people on a Western diet high in fructose often have high levels of uric acid in their blood. It was recognized that the metabolism of fructose in the body might cause increased production of uric acid, which then may impact the intensity of lipogenesis and the development of metabolic syndrome (MetS), insulin resistance, gout, cardiovascular diseases, leptin resistance, non-alcoholic fatty liver disease, or some combination of the above. To date, the treatment of hyperuricemia has been the recommendation of a low-purine diet characterized by limiting protein-containing products and certain alcoholic beverages, in addition to consumption of tart cherry or the widely prescribed purine analog and xanthine oxidase inhibitor allopurinol in an attempt to decrease endogenous uric acid production. However, these recommendations often contribute to an increased intake of carbohydrate-rich foods that may contain fructose or high fructose corn syrup (HFCS) constituents. Increased fructose consumption may then enhance the secretion of uric acid and, consequently, attenuate or negate any potential therapeutic effects from the prescribed therapeutic regimen. A better option instead of a low-purine diet for some would be to follow a healthy meal plan such as DASH or the Mediterranean diet, which can also benefit metabolic parameters. This article provides an overview of this approach, focusing on MetS and hyperuricemia among high-fructose dieters.

Keywords

Fructose, Uric Acid, Gout, Metabolic Syndrome, Fructosamine, Diet.

Introduction

Many health care providers, including physicians and nutritionists recognize the various contributions of inappropriate dietary intake and poor nutritional practices in the pathophysiology of development of numerous illnesses and diseases. The iterations of the traditional food pyramid that have evolved over the past several decades have emphasized the importance of including an abundance of fruits and vegetables in one's diet, while limiting the proportions of fats, sweets and salt in addition to the inclusion of a daily exercise regimen to promote a healthy diet and lifestyle. However, as dietary recommendations continue to change as more research has become available, some practitioners may struggle to keep abreast of the latest findings and incorporate them into their daily activities and clinical practices [1-3]. The recommendation of a diet low in purines is commonly recommended for patients presenting with hyperuricemia, metabolic syndrome (MetS), and related disorders, while failing to address the potential contributions of typical recommendations for which sweeteners may be the most healthful to incorporate into the dietary component.

Because many flavorings are lipid soluble constituents, the lipids contained in the diet may enhance their lingual presentation. The widespread commercial use of HFCS sweeteners is designed to improve the sweetness and overall palatability of the diet in the absence of abundant fats, while proposing to decrease the metabolic risks of comorbidities that may occur in the presence of hyperuricemia and MetS.

The emergence of high fructose corn syrup sweeteners in the food supply over the past several decades has now become a major source of fructose in the diet and has become an issue of significant concern to many practitioners due to its capacity to increase plasma fructose and fructosamine concentrations [4,5]. Such considerations include the inadvertent fructosyl glycation of plasma proteins in addition to its contributions to the formation of excess uric acid, hyperuricemia, and gout as plasma concentrations exceed the capacity for renal clearance of the metabolite. Free uric acid has limited solubility in aqueous solutions including plasma, which contribute to its potential to form inflammatory crystals in peripheral tissues when the plasma concentrations exceed the limits of solubility.

Solubility limits typically occur when uric acid levels exceed a consistent mean of approximately 7-8 mg/dl of fluid under physiologic conditions. Uric acid concentrations are sensitive to conditions of pH and temperature, both of which also impact net uric acid solubility in plasma and tissues and contribute to its potential to form inflammatory crystals in susceptible tissues [6,7].

Uric acid is an organic acid and is cleared by the renal tissues along with other organic acids via the process of competitive secretion. Because the mechanism of renal uric acid clearance for uric caid relies on secretion along with other organic acids, metabolites and toxicologic mechanisms, it may therefore compete with other organic acids and entities in the renal secretion process. Thus, careful attention should be addressed in monitoring the amount of HFCS and other fructose containing constituents of the diet that may increase the renal load of organic metabolites including uric acid. The recommended safe and healthful daily fructose intake is not entirely defined; however, 25–50 grams a day is often indicated as safe, with 50–100 grams a day as being high, and over 100 grams a day as potentially dangerous for human consumption. Greater amounts may exceed the capacity for luminal absorption and frenal clearance, in addition to contributing to symptoms of gastrointestinal discomfort. [2-4,7]. Because uric acid may exceed plasma solubility limits when plasma uric acid concentration exceed the capacity for renal excretion, typically in the range of approximately 7 mg/dl or more over an extended duration for most individuals, it can facilitate sharp urate crystals to precipitate in joints and other locations, cause inflammation, and the long-lasting exposure may inflict damage on the body in addition to the clinical diagnosis of gout. A plasma uric acid concentration of 7.0 mg/dl and above has long been considered an established clinical risk factor for the development of gout [1-3,7].

Plasma uric acid concentrations may be influenced by several factors

While the disorder of Gout is among the oldest known recorded metabolic disorders, and has been noted historically for centuries, the pathophysiologic mechanisms leading to its expression and development only became fully recognized since the middle of the last century as the pathways of intermediary metabolism became more widely known [1-3,6,7]. The cells and tissues of the body undergo continuous regeneration throughout most if not the entire the lifespan, and the metabolic products of the cellular turnover generate remnants of proteins and nucleic acids that include purine moieties that now become the substrate for urate formation [6]. The endogenous breakdown is additive to popular dietary sources that may also be rich in purines and uric acid substrates that also include dietary fructose, and thus their combined digestion and metabolism can become additive to the endogenous purring load [8-11].

The contribution of the various sources of uric acid substrates is depicted in Figure 1 below, and indicate that dietary fructose and intermediary metabolism represent the two largest contributors to the formation of uric acid, while high purine foods represent the smallest contributors, but still contribute an important proportion of the total substrate sources. Thus a diet high in purines can increase plasma uric acid concentrations, where they typically represent 1-2 mg/dl of the total plasma concentrations, while the combined impact of dietary fructose an other contributors to intermediary metabolism constitute over three fourths of the total uric acids produced daily. Therefore, all 3 sources of uric acid contributions must be addressed when planning an effective diet plan. The low purine diet, in combination with moderation of fructose intake remain the cornerstone of diet planning adjuncts in the therapeutic regimen for gout, as collectively they can potentially eliminate nearly 40% of the metabolic sources of uric acid generation, leaving only intermediary metabolism for the remainder. In addition, the combined impact of addressing the multiple sources of uric acid may exert a favorable effect on insulin sensitivity in various tissues [10-12].

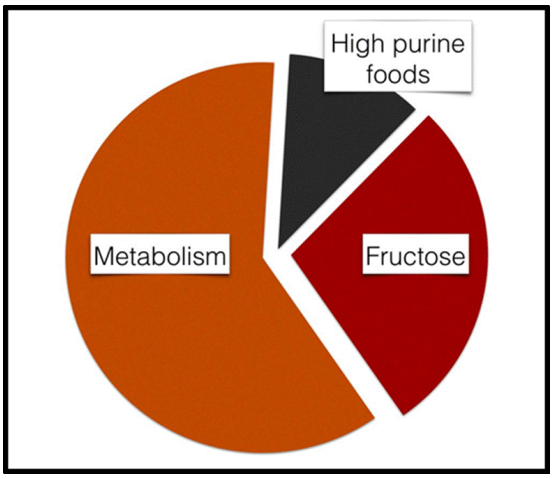

Figure 1: Impact of different metabolic factors on the uric acid concentrations.

Metabolic pathways of uric acid overproduction

A common observation of gout sufferers' points to an overproduction of uric acid in those individuals. Among the drivers to this impression are excess intake of purine rich foods in addition to an excessive intake of fructose containing foods and beverages, including certain alcoholic beverages [4]. Fructose, in the form of high fructose corn syrup sweeteners may contain up to 70% or more fructose as a percent of the total carbohydrate, and can add significantly to daily fructose consumption through common food and beverage sources. This occurs because HFCS is widely used in commercially manufactured edible food and beverage preparations to improve flavor, sweetness and overall palpability. In addition, it is a cost effective ingredient that can result in cost saving measures during their commercial production and manufacture. Thus, for the aficionado that may consume excessive amounts of sweetened beverages, it is easy to ingest 25% or more of one's total dietary caloric intake in the form of fructose during the course of a day and approach the metabolic capacity for the degrative biochemical pathways in energy metabolism [4,13]. These pathways include a bypassing of the normal insulin-dependent GLUT4 pathway which normally regulates the uptake of glucose in peripheral tissues [6]. When fructose uptakes challenge their capacity for oxidative metabolism, the substrate overage provides a ready access to uric acid generation as depicted in Figure 2 below. In addition, while excess fructose once phosphorylated becomes compartmentalized in intrcellular locations where it may contribute to the biosynthesis of fatty acids, triglycerides, and non-alcoholic fatty liver disorders (NAFLD) [6,12-14]. The more expeditious fate for excess fructose disposal is the formation of uric acid from AMP degradation and concurrent depletion of cellular ATP availability.

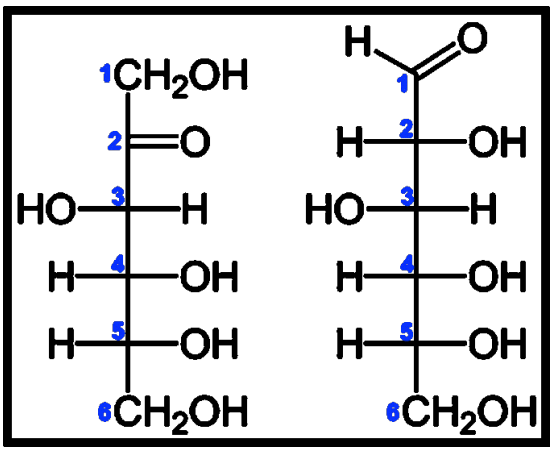

Figure 2: Fischer projections of d-fructose (left) and d-glucose (right) empiric formula $C_6H_{12}O_6$ for both moieties [13]. The d-configuration is determined but the position of the OH on the right side of the penultimate (C5) carbon for a C6 carbohydrate [6].

Metabolism of carbohydrates: fructose and glucose

Fructose is a commonly available and naturally occurring carbohydrate source, where it is typically found in numerous fruits, vegetables, and honey, and can be absorbed in tissues without a significant surge in plasma insulin [12,13]. Changes in the agrifood industry over the past several decades introduced the efficient methods for the manufacture or high fructose corn syrup (HFCS), which may now contain over 70% fructose as a carbohydrate source. Fructose has a glycemic index of 32 compared to glucose or sucrose (~100), thereby increasing its preference as a generally considered safe and healthy cost-effective sweetener when obtained from natural or commercial sources. In addition, its other favorable characteristics include its diverse functionality as an ingredient in food preparation. [14.]. These changes in the commercialization of fructose in the food industry have been associated with significant increases in daily fructose intake from a previous level of 16-24 g/day to over 80 g/day, approaching the safe limit for human metabolism [4,5,15].

Structurally, both the C_2 ketose sugar fructose and -C_1 aldehyde form glucose have a similar configuration and empiric formula ($C_6H_{12}O_6$) .with a primary difference at the level of carbon number 2 (Figure 3). In fructose the hydroxyl is replaced by a ketone, thereby imposing a stereospecific receptor failure for the insulin dependent GLUT4 receptor

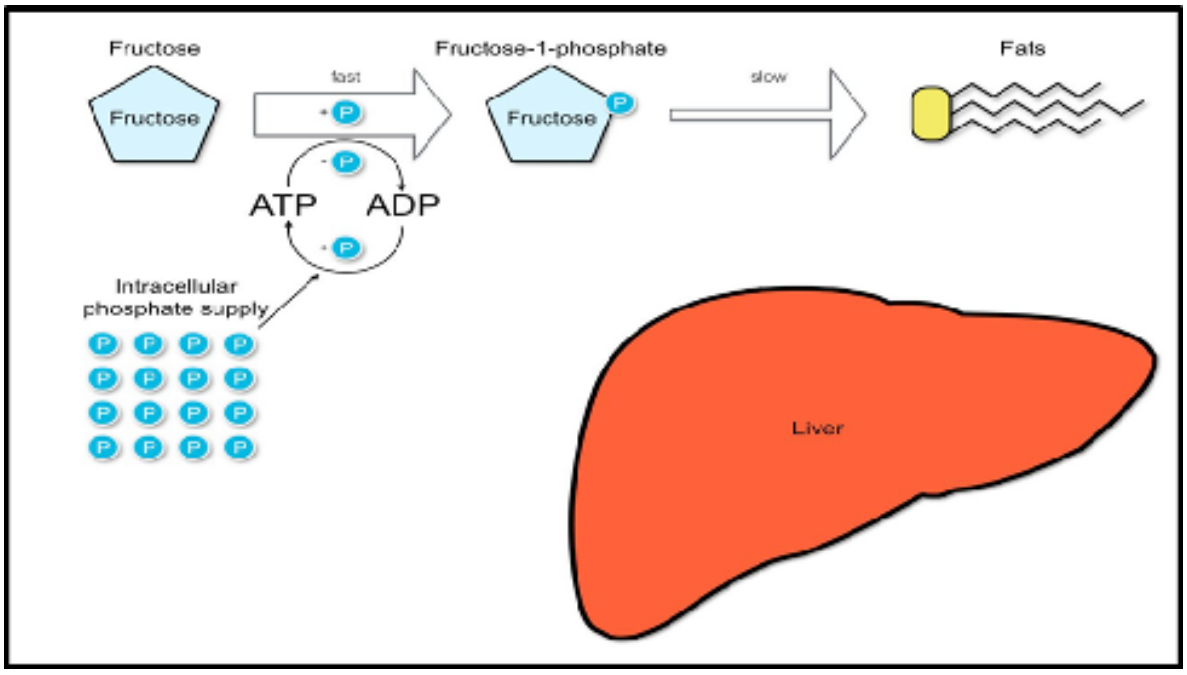

Figure 3: Schematic overview of fructose disposal in the liver. ATP = adenosyl triphosphate; ADP = adenosyl di phosphate; Fast = hexokinase; fats depicts fatty acids and triglycerides [adapted from 6].

and transport mechanism that normally occurs for glucose. Fructose enjoys its own class of GLUT transporters, specifically the GLUT1 and GLUT5 transporters, which not only facilitate glycemic transport more slowly than the activated GLUT4, but also function independently of insulin actions all while enjoying a greater measure of sweetness [4,6]. In nominal amounts contained in natural sources including fruits, vegetables and honey, fructose is not known to be harmful, and is considered to exert a neutral impact on aspects of carbohydrate metabolism.

Because dietary fructose cannot undergo direct oxidation and metabolism in most tissues, it must first undergo phosphorylation to become fructose-1 phosphate, after which it may become further metabolized in the liver as depicted in Figure 3 and in liver, muscle and adipose tissue in Figure 4 respectively, As depicted in Figure 3, fructose consumes abundant amounts of high energy phosphates in the form of ATP during the irreversible cytosolic conversion to fructose 1 phosphate. Since once the sugars become phosphorylated compounds, the reactions are non-reversible thereby providing ready intracellular substrates for subsequent stereospecific, oxidative reactions to their endpoints of ATP and CO2 or conserved as triose phosphates, lactate, and fatty acids and triglycerides during lipogenesis [6,16-19].

The aerobic oxidation of d-glucose remains the preferred carbohydrate substrate for cellular oxidation however, and energy metabolism in most tissues, efficiently yielding an average of 32-38 ATPs per molecule of oxidized substrate in muscle and liver tissues (Figure 4). While the net yield of ATPs from oxidation of fatty acid molecules is greater, the process of mobilization of fatty acids from triglyceride is inhibited in the presence of hyperinsulinemia, thereby supporting it's role as a secondary energy source when sources of carbohydrate moieties including glucose or fructose become limiting [6]. In the upper section of Figure 5, the phosphorylation of fructose and glucose is depicted, including shared steps during its conversion to acetyl CoA. During normal metabolism, energy demands the majority of energy needs of an organism are met via the process of glycolysis from glucose in a closely regulated process, such that the process of glycolysis is closely matched to intrinsic energy demands. This process succeeds and survives because of the inhibition of phosphofructkinease in the glycolytic pathways by intracellular citrate and ATP concentrations, in addition to the non-reversible nature of the hexokinase enzyme by phosphorylated intermediates and the net loss of molecular energy as the substrates undergo progressive steps during their metabolism. In hepatocytes however, the fructose phosphates are split into triose phosphates that can be converted into acetyl-CoA and lactate and thus can become available for both gluconeogenesis and fatty acid synthesis [6].

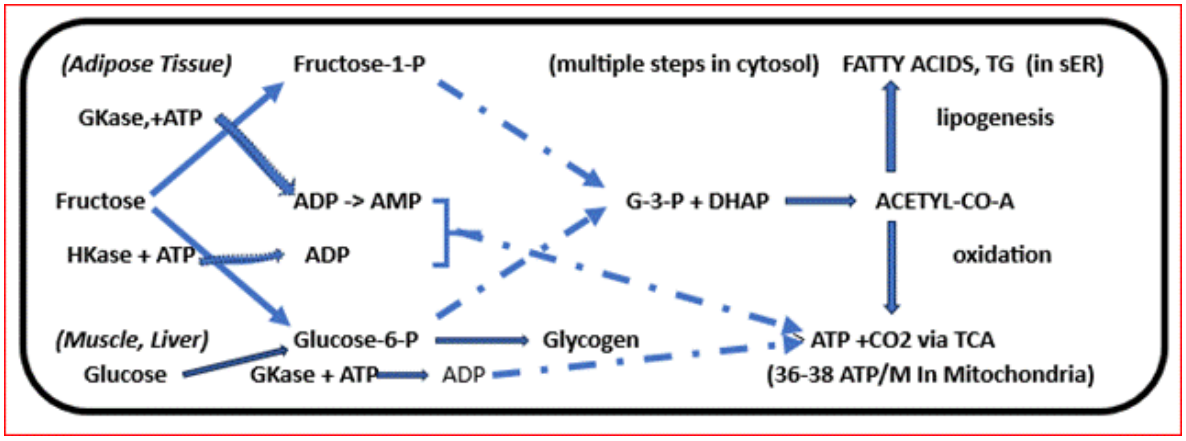

Figure 4: Schematic of fructose and glucose metabolism in muscle, liver and adipose tissue (modified, from 1), HKase = hexokinase, fructokinase; GKase = glucokinase. G-3-P = glyceraldehyde 3 phoshate; DHAP = dihydroxtacetone phosphate; ATP = adenosine triphosphate; ADP = adenosine diphosphate; AMP = adenosine monophosphate; P = phosphate. (Developed from 11,13). Broken lines indicate multiple steps. TCA = citric acid cycle. sER = smooth endoplasmic reticulum. Developed from [6].

When large quantities of fructose are presented to the liver depicted in Figure 5, the overage may exceed the usual degradative and oxidative capacity for pathways for fructose metabolism, resulting in a limitation in the availability of ATP at least in part to diminished intracellular availability of inorganic phosphate for ATP regeneration. As phosphate becomes limiting, ADP and AMP accumulate, providing substrates for AMP degradation, thus, by generating a fructose-induced intracellular phosphate deficiency, the process of uric acid formation becomes set in motion. By producing a relative deficiency in ATP availability, coupled with an increase in AMP due to phosphate depletion, the resulting progressive degradation of purine bases of ADP to AMP, IMP, inosine, xanthine, and hypoxanthine, become increased, thereby generating the metabolic precursors for uric acid as an end-product of AMP catabolism. Thus, the overuse and increased utilization of fructose and fructose containing sweeteners in manufactured foods and beverages remains a plausible source of excess uric acid formation as a contributor to gout [20-23].

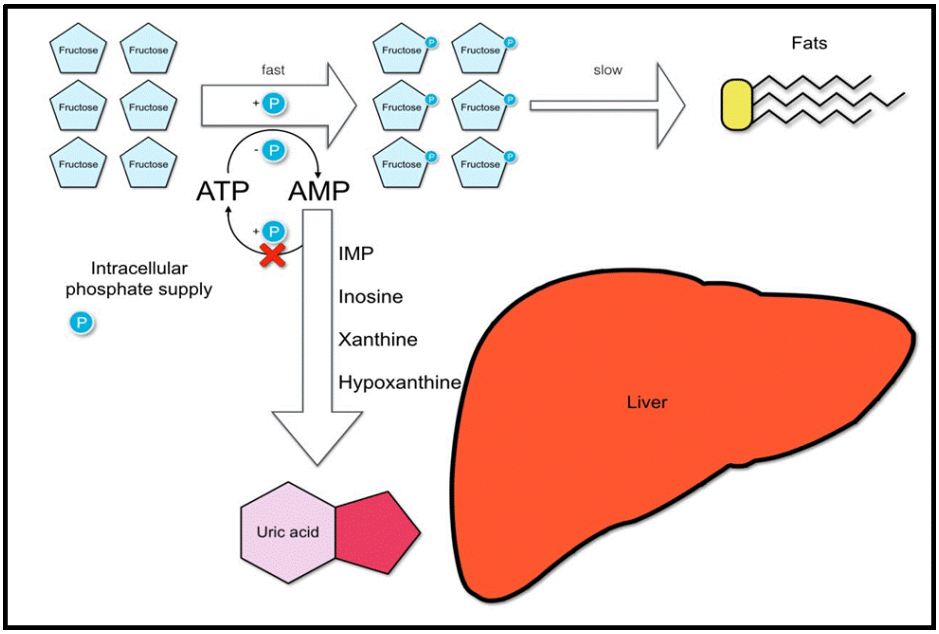

Figure 5: Fructose metabolism of large quantities of fructose. Fast = hexokinase; ATP = Adenosine triphosphate; AMP = adenosine monophosphate; IMP = inosine mono phosphate;. Fats – fatty acids, triglycerides. Adapted from [6].

Thus, as depicted in Figure 5, a diet containing excess proportions of fructose and fructose containing sweeteners may become problematic for gout sufferers. Fructose as a limited normal constituent of fruits and vegetables has always likely been a minor constituent of the human diet, where it occurs in combination with dietary fibers, gums and other dietary components that collectively slow its rate of luminal absorption and postprandial disposal. However, the commercial production and use of high fructose sweeteners in manufactured foods and beverages while improving their palatability, may drastically increase daily consumption to 25% or more of daily caloric needs. In higher amounts, it may place a strain on the capacity for efficient metabolism in the liver and other peripheral tissues, with an unfortunate endpoint in overproduction of uric acid. The maximum plasma solubility of uric acid occurs in the range of 7 to 8 mg/dl, after which the excess uric acid mat precipitate in susceptible tissues. In the US, estimates of 330-380 kcal of fructose intake are common with greater amounts clearly problematic, and contribute to hyperuricemia [7-10].

In addition to gout, hyperuricemia also has been associated with hypertension, diabetes, overweight and obese conditions, MetS, and renal failure [8,13,14,16]. The presence of hyperuricemia is a bidirectional causal factor in the above disorders, which can also further aggravate the pathophysiology of their progression [24]. The conditions associated with hyperuricemia are summarized in Table 1.

Table 1. Diseases associated with symptomatic and asymptomatic hyperuricemia and their general mechanism of action

Symptomatic Hyperuricemia		
>Gout	Stones in the Urinary Tract	[25]
Asymptomatic Hyperuricemia		
Chronic kidney disease	• Deposition of sodium urate crystals • Oxidative stress • Endothelial dysfunction • Fibrosis and inflammation of the kidneys	[10,5,3,26]
Type 2 diabetes mellitus	• Induction of pancreatic beta cell death • Weakened insulin signaling	[24,25]
Cardiovascular disease	• Inducing inflammation • Endothelial dysfunction • Proliferation of vascular smooth muscle cells • Activation of the renin–angiotensin system • Oxidative stress	[13,24]
Obesity	• Weakened insulin signaling • Excess of FFA • Oxidative stress • Inflammation	[13,25-27]

Adverse effects of Fructose

While fructose also does not produce a significant insulin surge when compared to glucose or sucrose, high dietary levels of fructose ingestion have been linked to elevated body weights, adiposity, and serum fructosamine concentrations in man and animals. In experimental studies in both lean and obese phenotypes of the corpulent rat, elevations in blood glycosylated hemoglobin were observed in the lean phenotype of the congenic NIDDM-prone SHR/N-*cp* rat strain and increases in serum fructosamine developed both phenotypes following fructose feeding regmens [23]. These effects were similar to the effects of sources of excess fructose consumption in humans, and suggest caution may be exercised for high fructose intakes in diabetes, despite its ability to be absorbed independently of insulin-dependent actions [6,22,23]. Because several reports implicate the adverse effects of excess fructose consumption as a contributor to hyperuricemia and gout, it is worthy of consideration to add dietary fructose consumption limits in dietary planning for the clinical management of gout and gout-prone conditions. Once a clinical diagnosis has been established, treatment and management for gout often continues indefinitely, where the xanthine oxidase inhibitor and purine analog allopurinol is among the most commonly prescribed medication of choice [28]. The drug inhibits xanthine oxidase, which catalyzes the final steps in the formation uric acid, there by allowing the renal excretion of the more soluble purine precursors [28-30]. The specific diseases and conditions where allopurinal may be used effectively include gouty arthritis and idiopathic gout, resolution of skin tophi, kidney stones, and uric acid lithiasis among numerous other conditions linked to hyperuricemia [14-19, 31-44].

Because fructose is found in many common dietary sources, reports often raise the issue of whether normal dietary sources of fructose may contribute to hyperuricemia and gout [14,45]. An important aspect of these considerations however is the observation that fruits and other normal dietary sources of natural sugars, apart from fructose, also contain many other health-promoting compounds, such as vitamins, flavanols, fibers and gums, and a plethora of trace elements that can modify the potentially adverse effects of fructose [46]. Ayoub-Charette et al. [47] showed that there is no statistically significant relationship between fruit consumption and gout in a meta-analysis of multiple studies, with the exception of consumption of fruit juices high in fructose content that occur mostly in the form of HFCS. In addition, most commercially prepared juices commonly lack dietary useful fibers and other constituents typically present in the fresh produce [48,49]. Orange juice is among the most widely consumed juice products worldwide, often touted for it content of vitamin C, but also containing HFCS sweeteners [47-50].

Kambay et al reported that both the amount of fructose contained in manufactured and processed beverages, in addition to the rate of consumption by consumers contribute to the magnitude of the fructose load, and noted that due to the numerous other constituents of fresh produce moderate rates of luminal fructose absorption. In addition, the rate of fructose absorption occurs more slowly and within safer limits when obtained from natural vs commercially prepared juices, thereby minimizing the potential added risks of fructose overload [47-50]. As an extension of the metabolic impact of excess fructose ingestion, elevations in plasma fructosamine may occur via a nonreversible, non-enzymatic Maillard reaction with plasma proteins in a dose-related manner, thereby decreasing their physiological activity [4,5,22,23].

Conclusion

The commonly prescribed low-purine diet often recommended for hyperuricemia and gout may not always be an appropriate or exclusive choice of nutritional management for hyperuricemia. Further considerations of sources of dietary fructose, including foods and beverages containing HFCS should therefore also be included in the dietary planning regimen. Failure to recognize the metabolic impact of excess fructose intake may worsen both the metabolic and pathophysiologic parameters of hyperuricemia and potentially compromise the effectiveness of its clinical treatment. One solution may be the incorporation of the Mediterranean diet or the DASH diet, which typically exclude abundant sources of foods that contain dietary fructose. It may be concluded that the influence of high levels of uric acid and fructose on the individual parameters of MetS may be significant and requires further research to understand the more precise pathophysiologic and interrelated mechanisms of disease formation and the possibility of more effective planning of their treatment.

In the literature, the question arises more often about examining individual sources of fructose and their impact on the induction of hyperuricemia and the MetS syndrome. Attention is also drawn to the need to study unique populations depending on sex, age, or geographic location to obtain more accurate results and delve more deeply into the individual elements of fructose metabolism. An interesting aspect in this area could be analyzing a comparison of two groups of patients with hyperuricemia on a low-purine diet and a DASH/Mediterranean diet to examine their metabolic parameters and uric acid levels after carefully planned menus. This would enable one to examine the effect of consuming large amounts of high-fiber products with the simultaneous use of fructose-rich products other than fruits and vegetables. It could help assess the impact of fiber, polyphenols, antioxidants and other dietary constituents on fructose metabolism. Further study is needed to fully resolve these questions.

In conclusion, a substantial body of evidence derived from scientific investigations confirmed the fructose consumption in Westernized societies has increased dramatically in recent decades. In addition, the metabolic contributions of excess dietary fructose consumption in its various nutritional forms is a likely significant contributor to hyperuricemia and its progression to the development of gout and other metabolically related disorders. Because the typical dietary daily intake of fructose has increased 4- to 5-fold in recent decades, where it now may account for up to 25% or more of one's daily caloric intake. The significant increase in fructose consumption is likely due in large part to the widespread incorporation of fructose in its various dietary forms in commercially manufactured foods and beverages. The various fructose sources that are now established constituents of commonly consumed foodstuffs, including popular juice drinks and sweetened beverages. The increases *per capita* consumption patterns indicates that an emerging need is rapidly approaching to reassess the role of dietary sources of fructose in the pathophysiology of metabolic illnesses. Metabolic disorders including obesity, NIDDM and metabolic syndrome (MetS) are currently approaching epidemic proportions in Western society and are contributing to additional strains on the burden of health care resources for their management and cost- and resource-efficient delivery. Dietary solutions represent an essential adjunct in their clinical management and control.

Acknowledgements

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Conflict of interest

The authors declare that there is no conflict of interest.

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