The Role of Dietary Sugars and Sweeteners in Metabolic Disorders and Diabetes

Motahar Heidari-Beni and Roya Kelishadi

Contents

Abstract

Sugar consumption has dramatically increased worldwide. A growing body of evidence suggests that sugars might have various adverse health effects. High intake of sugars may be related with an increased risk of several disorders including dental caries, obesity, cardiovascular disease, diabetes, gout, fatty liver disease, some cancers, components of the metabolic syndrome, and

M. Heidari-Beni (✉)
Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran
e-mail: heidari.motahar@gmail.com; motahar.heidari@nutr.mui.ac.ir

J.-M. Mérillon, K.G. Ramawat (eds.), *Sweeteners*, Reference Series in Phytochemistry,
DOI 10.1007/978-3-319-26478-3_31-1

hyperactivity. Added sugar in processed foods are used to sweeten, to increase the flavour, to change the freezing or melting point or to protection of food spoilage. It is better to consume sugars in natural foods, since these foods provide useful micronutrients. Nowadays, there are questions as to whether excessive consumption of sugars, especially processed foods, might be correlated with metabolic syndrome or diabetes. However, insufficient study design, variety in evaluating dietary intake, contradictory findings and several definitions of sugars have inhibited definitive conclusions regarding these associations. However, limiting added sugars and monitoring carbohydrate consumption are serious strategy for keeping healthy weights and achieve glycemic control. This chapter describe different types of sweeteners in foods and beverages, as well as their effects on diabetes and metabolic disease. In addition, this chapter describes underlying mechanisms of sweeteners on health outcomes and how various types of sweeteners may threaten health.

Keywords

Sweeteners • Non-nutritive sweeteners • Sugar sweetened beverage • High-fructose corn syrup • Diabetes • Metabolic syndrome

Abbreviations

FAO	Food and agriculture organization
GI	Glycaemic index
GL	Glycemic load
GLP	Glucagon-like peptide-1
GLUT	Sodium-glucose transport proteins
HFCS	High fructose corn syrup
HPFS	Health professionals follow-up study
IMP	Inosine monophosphate
KHK	ketohexokinase
NHS	Nurses' health study
NNS	Non-nutritive sweeteners
NS	Natural sweeteners
SSB	Sugar-sweetened beverages
T1R	Taste receptors type 1
XO	Xanthine oxidase

1 Introduction

Quality of life is markedly dependent on taste sensory system. We select foods primarily according to sentimentality of pleasure or displeasure experienced of their taste. Studies showed that sweet was an innately preferred sensation.

Carbohydrates are the main source of food energy. They are remarkable for their structure and well taste, which in sugars is sweet. Carbohydrates have two forms including complex molecules especially starches, dextrins and fibre or simple

carbohydrates that generally called sugars. Fruit, some vegetables, milk, soft drinks and sweets are the main dietary sources of sugars. Structure of sugars is called monosaccharide. Glucose (also called dextrose), fructose, and galactose are monosaccharides. Disaccharide is formed by combination of two monosaccharides. For example, combination of glucose and fructose form disaccharide sucrose or table sugar. Two glucose molecules compose maltose and one molecule of glucose and one molecule of galactose make lactose (milk sugar). All sugars are carbohydrates and contain four calories per gram. The amount of sugars intake is so important in the daily diet. Sugars supply the rapid source of glucose for brain (cognitive functions) and muscles (physical activity) [1, 2].

Added sugar in processed foods are used to sweeten, increase the flavour, change the freezing or melting point or to protection of food spoilage. It is better to consume sugars in natural foods, since these foods provide other micronutrients. Nowadays, there are questions as to whether excessive consumption of sugars especially processed foods might be correlated with metabolic syndrome or diabetes [3, 4].

In a healthy diet, all types of carbohydrates must be consumed. According to recommendation of The Food and Agriculture Organization (FAO) and WHO, sugars or simple carbohydrates must be intake less than 10 % of the total caloric value of the diet. Sugars must be part of a healthy diet with limited consumption of sugar-sweetened drinks. Also, for achievement greater benefits, it has been recommended that consumption of sugars or sugar- sweetened foods must be limited to less than three times/day not exceeding 6 % of total energy intake [5].

2 Concepts of Sugars and Sweeteners

Sugar has been in human diets since ancient times. Earliest consumption has been reported from China and India and after that from Europe after the Crusades in the eleventh century. Natural dietary sugars (fructose, sucrose, and lactose) and added or extrinsic sugars (sugars and syrups that are added to foods and beverages during processing and preparation) are found in many foods. Over the past three decades, intake of sugars has dramatically increased in United State. The main reason of this increase is driven by high fructose corn syrup (HFCS) intake, that now consumption of HFCS is over 62 lb per person per year mainly in the form of sugar-sweetened beverages (SSB) [6, 7]. SSBs include soft drinks, fruit drinks, energy and vitamin water drinks. They are composed of naturally derived caloric sweeteners such as sucrose (50 % glucose and 50 % fructose), HFCS (most often 45 % glucose and 55 % fructose), or fruit juice concentrates [8].

According to evidence, sugars might have adverse effects on health condition. High intake of sugars may be related with an increased risk of dental caries, obesity, cardiovascular disease, diabetes, gout, fatty liver disease, some cancers, components of the metabolic syndrome and hyperactivity [9–12]. However, insufficient study design, variety in evaluating dietary intake, contradictory findings and several definitions of sugars have inhibited definitive conclusions regarding these associations [13].

Table 1 Classification of sugars and sweeteners

Natural	Caloric	Sugars	Sucrose Glucose Galactose Fructose Lactose Maltose Trehalose
		Others	Honey Maple syrup, Palm sugar, Coconut sugar
Artificial	Caloric	Modified sugars	(High fructose) corn syrup Inverted sugar
		Sugar alcohols	Sorbitol Xylitol Mannitol Lactitol
	Non-caloric	Artificial sweeteners	Aspartame Sucralose Saccharin Neotame, Acesulfame K Cyclamic acid Alitame Advantame

There is metabolic interaction between different sugars, for example between fructose and glucose. When fructose ingests alone has different metabolic effect in comparison with consumption together with glucose. Fructose intolerance arise when it is consumed alone, however intolerance symptoms disappear when it consume with glucose. In addition, fructose intake alone leads to glycogen synthesis less than when fructose consumed with glucose [14].

There are different ways for classification sweeteners; using the glycaemic index (GI) or their energy contribution. Based on energy contribution, sweeteners are classified as "caloric" or "low calorie/non-caloric" or as "nutritive" or "non-nutritive" (Table 1) [3, 15].

3 Activation of Sweet Taste Receptors

Nutritive sweeteners and non-nutritive sweeteners (NNS) evoke sweet taste sensation in mammals. Sweet taste receptors type 1 (T1R) subunits 1 (T1R1) and 3 (T1R3) detect sweet sensation. These receptors are coupled to α-gustducin, a transducin-like heterotrimeric G-protein [16]. There is T1R in the lingual taste buds and also in the enteroendocrine cells of the small intestine that are involved in Glucagon-like peptide-1 (GLP-1) secretion [17]. Studies showed when intestinal

T1R2 and T1R3 were activated by acesulfame-K, sucralose and saccharin in mice, upregulate the expression of the Na^+ dependent glucose transporter SGLT1. In turn, activation of this transporter enhances intracellular Ca^{2+} concentrations and consequently the translocation of the facilitative glucose trans-porter GLUT2 into the brush border membrane of the enterocyte [16–18]. In addition to, the promotion of intracellular Ca^{2+} levels activates a member of the transient receptor potential melastatin (TRPM), TRPM5, which is co-expressed with T1R in enterocytes and functions as a downstream component in sweet taste signal transduction pathway. TRPM5 activation then promotes Na^+ influx, whose role, although not understood yet, could hypothetically facilitate SGLT1-mediated glucose transport. As a whole, these data suggest that NNS leads to an increase in the intestinal absorptive capacity of glucose and consequently of its blood levels, eventually favoring an hyperglycemic state in NNS-exposed neonates. Interestingly enough, activation of T1R present in GLP-1-secreting cells can stimulate the secretion of incretins, which in turn increase insulin secretion, appetite and weight gain [19].

4 Types of Sweeteners

4.1 Non-Nutritive Sweeteners (NNS)

Consumption of NNS has increased among people of all ages. 28 % of total population reported NNS intake that this amount is highly prevalent in children. Most of the NNS-containing foods intake among population is NNS-containing beverage. According to National Health and Nutrition Examination Survey, consumption of NNS-containing beverage increased from 6.1 % to 12.5 % among children and from 18.7 % to 24.1 % among adults [20]. Some foods contain NNS including beverage, ice cream, yogurt, chewing gum, chocolate, jams and chocolate. There has been much debate regarding the health advantages and disadvantages of artificial sweeteners [21].

NNS, also refer as very low-calorie sweeteners, artificial sweeteners, non-caloric sweeteners, and intense sweeteners. These sweeteners have a higher sweetness taste than caloric sweeteners such as sucrose, corn syrups and fruit juice. NNS are added in smaller quantities and provide no or few calories, no glycaemic effect and high sweetening power [22]. Among NNS, saccharin is prominent. It has great sweetening intensity. In addition to, Sucralose and aspartame are remarkable for their wide worldwide use, particularly in beverages. Methyl ester of phenylalanine and aspartic acid are components of aspartame. Its use is approved by the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) [23, 24].

Currently, six sweeteners use in foods and beverages in US that are approved by the Food and Drug Administration (FDA). These sweeteners including aspartame, sucralose, saccharin, acesulfame potassium, neotame and advantame, with two plant-derived sweeteners (steviol glycosides, and Luo han guo extract) [25]. In most cases, these sweeteners provide little or no energy because they activate receptors of sweet taste at very low concentrations in comparison with sugar

[26]. Although these sweeteners have various chemical structures, they can activate some of the multiple potential ligand binding sites of the heterodimeric T1R1 + T1R3 sweet-taste receptor in human subjects [27].

NNS provide little or no energy, so when NNS are used in place of caloric sweeteners in foods and beverages, the amount of calories intake will be reduced while maintaining high palatability. NNS provide sweet taste without calories or glycemic effects, so it is commonly believed that NNS are healthy substitutes for sugars [25]. However, scientific evidences do not actually support such a belief and there is a great deal of debate regarding the health consequences of NNS intake [26]. Studies suggested that NNSs are not physiologically inert, and may influence feeding and metabolism by different peripheral and central mechanisms [28].

Some studies showed positive relationship between NNS intake and weight gain, metabolic syndrome, and type II diabetes [29, 30], although other studies did not show any association [31, 32]. Nevertheless, several reviews and meta-analyses of epidemiological and experimental studies could not show a consensus result. Some studies reported potentially beneficial [33], harmful [34], or trivial [35] effects of NNSs. Taken as a whole, despite numerous studies showed an association between NNS intake and metabolic disorders in animal models [36, 37], there is no sufficient evidence in human subjects. However, findings from at least five various mammalian species (rats, mice, cows, pigs, human) reported that NNSs could be metabolically active [38, 39]. More research is needed to clarify the mechanisms of metabolic and potential effects of NNSs as commonly used food additives [25].

4.2 Proposed Mechanisms Underlying NNS Metabolic Effects

Physiological studies observed NNS decreased the release of the incretin hormone GLP-1. This hormone implicates in food intake regulation, blood sugar levels and protection of the cardiovascular system. When GLP-1 levels persistently decreased through intake of artificial sweeteners, risks of diabetes, cardiovascular disease and stroke would be increased in long term [40].

Modulation of the intestinal microbiota is another potential mechanism to illustrate the relationship between NNS intake and adverse metabolic outcomes. The intestinal microbiota of humans and rodents include only a few dominant and commensal bacterial phyla, exclusively Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria. These gut microbiota impact on important physiological functions of the host, especially immune system and dietary nutrients metabolism. A decrease in the proportion of Firmicutes has been found in type II diabetic patients and the proportion of Bacteroidetes has been decreased in obese individual in fecal samples [41, 42].

Animal studies showed that artificial sweeteners consist of saccharin, sucralose and aspartame modify gut microbiota and led to overeating, weight gain and impaired blood sugar regulation [43]. Findings of one animal study showed consumption of a mixture of sucralose with nutritive sweeteners decreased the number

of commensal bacteria including Bifidobacterium (phylum Actinobacteria), Lactobacillus (phylum Firmicutes) and Bacteroides (phylum Bacteroidetes). These effects have been associated with the development of insulin resistance, hyperlipidemia, enhanced adiposity and inflammation [19].

In addition to, in a small human study, saccharin led to gut microbiota alteration and blood glucose dysregulation. Taken as a whole, gut microbiota have many roles in health and disease. If artificial sweeteners consume persistently, disrupt gut microbiota composition and lead to some adverse effects including weight gain and glucose intolerance [26].

4.3 Natural Sweeteners (NS)

Natural caloric sweeteners consist of sucrose, fructose, glucose and maltose. Fructose has been substitute with sucrose in diabetic patients. Recently, however, it has been reported that high fructose diets, particularly when the fructose is added to processed foods, can induce hyperinsulinaemia, hypertriglyceridaemia and insulin resistance, and this has led to limit fructose use in diabetic patients [3].

5 Sugar Sweetened Beverage (SSB)

SSB consumption has been enhancing worldwide. SSBs have become common beverages that consume around the globe. SSB consumption rise among Asians, however, it is lower than Western populations. Traditional diet of Asian populations that consist of rice or grains as staples and abundant vegetables substitute with the Western lifestyle include meat and sweet foods as desserts and beverages. The average energy intake from SSBs has increased from 22.3 to 20.0 kcal/day in adolescents and young adults in 1998 to 35.1 and 29.4 kcal/day in adolescents and young adults in 2009, respectively. In addition to, sugar consumption from soft drinks is the highest between all types of beverages [44].

Over 70 % of adults consumed SSB include soft drinks or fruit drinks with added sugar with over 25 % reporting daily intake in 2012 [45].

Recently, numerous large-scale cohort studies have reported that SSBs, that commonly include soft drinks, fruit drinks, and sports drinks, are related positively with development risk of metabolic dysfunctions including type II diabetes and cardiovascular disease [44]. In contrast, a beverage contains 100 % fruit juice without any added sweeteners, is not recognized as SSB [46].

SSBs intake regularly has been directly related with variety of negative outcomes and adverse cardiometabolic effects, including weight gain and obesity, hypertension, diabetes, metabolic syndrome and stroke [47, 48]. According to recent meta-analysis, one serving per day increment in SSB intake was related to a 0.06 unit increase in body mass index in children and 0.22 kg weight gain in adults during 1 year [47]. Another meta-analysis found a clear association between SSB

consumption and risk of metabolic syndrome and type II diabetes. These findings provide further support to restrict intake of SSBs and substitute healthy alternatives including water to decrease risk of obesity-related chronic disease. High intake of SSBs lead to 26 % increase risk of diabetes and 20 % increase risk of metabolic syndrome [46].

In addition to, frequent SSBs drinkers consume more total and saturated fat, carbohydrate, sodium, lower fiber, dairy products and as well as they have a sedentary lifestyle. All of these factors can be related to increase risk of metabolic disease [48].

The powerful and consistent relationship between SSB consumption, obesity and some diseases including diabetes and metabolic disorders lead to increasing emphasis on decreasing the availability and intake of sugars and SSBs among children and adults [49]. However, in individual that intake persistently high level of SSBs, reduction of sugary foods and beverages consumption is not simple.

The substitution of artificial sweetened beverages for SSBs may be considered. While, there is lack of clear and consistent supporting evidence that show artificial sweeteners will promote healthy outcomes [50].

According to findings of interventional studies, substitution of artificially sweetened versions for sugar sweetened versions of foods or beverages did not consistently show that artificial sweeteners promote weight loss in overweight individuals. These results suggest that less effectiveness of artificial sweeteners in comparison with sugar sweeteners. In other words, artificial sweeteners do not appear to make better outcomes than sugar sweeteners. Recently one meta-analysis showed that artificial sweeteners may be useful for short-term weight loss [51].

Taken as a whole, evidence suggests that sugar sweetened beverages consumption is problematic. However the data regarding whether artificial sweetener beverages are particularly beneficial as replacements is vague [26].

5.1 Sugar Sweetened Beverages and Blood Pressure

Recently, one systematic review reported SSBs consumption was correlated with higher blood pressure, so, increased incidence of hypertension [52]. In addition to, a recent meta-analysis has found that total fructose intake did not increase risk of hypertension [53]. A recent study investigated relationship between SSBs and the incidence of hypertension on data from Nurses' Health Study (NHS) I and II, and Health Professionals Follow-up Study (HPFS) that are three large American cohorts. Findings showed that SSBs were correlated with an increased risk of incident hypertension. Also, findings of cross-sectional study from the US National Health and Nutrition Examination Surveys (NHANES) 1999–2004 [54] and 2003–2006 [55], and the International Study of Macro/Micronutrients and Blood Pressure (INTERMAP) showed a positive correlation among SSB intake and directly measured blood pressure [56].

5.2 Sugar Sweetened Beverages and Diabetes

One meta-analysis study based on data from eight prospective cohort studies consists of 310,819 participants and 15,043 type II diabetic patients showed participants in the highest category of SSB consumption had a 26 % greater risk of developing type II diabetes than participants in the lowest category of intake [46]. In the NHS II, a cohort of over 50,000 women, participants who intake more than one SSB per day had 83 % greater risk of developing type II diabetes during 8 years compared to those who consumed less than one per month after adjusting for potential confounders [32].

Meta-analyses study showed a clear positive correlation between both sugar sweetened and artificially sweetened soft drinks and the increasing incidence of type II diabetes. The relationship was stronger and more consistent for sugar sweetened soft drinks than artificially sweetened soft drinks. According to findings, increase of 330 ml per day being correlated with approximately 20 % increased risk of diabetes [57].

One 12 oz daily increase in SSB consumption was related with a 22 % development in the risk of type II diabetes in European adults [44].

5.3 Sugar Sweetened Beverages and Metabolic Syndrome

Metabolic syndrome has developed in Western countries. Its components are obesity with other abnormalities such as alterations in glucose metabolism, hyperlipidemia and hypertension. Findings showed 20–25 % of adult population in the world were diagnosed as metabolic syndrome. Obesity, unhealthy diet, and sedentary lifestyle lead to high prevalence of metabolic syndrome [58].

Study on 19,431 participants and 5,803 cases of metabolic syndrome (data from three prospective cohort studies) showed participants that consumed high amount of SSBs had 20 % greater risk of developing metabolic syndrome than those in the lowest intake [46]. Findings of one cohort study on 6,000 adults showed those who consumed more than one soft drink per day had 39 % greater risk of metabolic syndrome during 4 years [59].

Propensity of SSB to induce weight gain, rapidly absorption of large quantities of carbohydrates including sucrose or HFCS, rapidly enhance in blood glucose and insulin levels lead to metabolic consequences of SSB consumption. SSB often consume in the large volumes and contribute to a high dietary glycemic load (GL). According to findings, High GL diets stimulate appetite and lead to weight gain and are correlated with development of glucose intolerance and insulin resistance. In addition, high GL diets have been associated with lipid profiles abnormality and increase levels of inflammatory biomarkers including C-reactive protein that is a well-known marker for development of type II diabetes and cardiovascular disease risk [60].

Most epidemiological studies that investigate the association between SSBs and metabolic diseases have been carried out in Western populations and a few studies

have considered Asian populations [44]. However study in Taiwan showed high SSB consumption associated with 1.9 and 2.7 times higher risk of metabolic syndrome in boys and girls, respectively [61]. One cohort study suggested that approximately one cup of soft drink per week was correlated with a 17 % higher risk of metabolic syndrome in Korean populations [62].

6 High-Fructose Corn Syrup (HFCS) and its Relationship with Health

Fructose is generally called as fruit sugar because it presence in fruits. Fructose use in different forms including crystalline form in corn starch, liquid form in honey or liquid high-fructose corn syrup (HFCS) when combined with glucose. HFCS is used in the preparation of several beverages. Fructose is absorbed in the intestine and 60–70 % of fructose is transported to the liver. Other 30–40 % of fructose is transported to the kidney, adipose tissue and other organs. Fructose consumption has enhanced in countries adopting a Western diet during the past three decades. Although fructose has a lower glycemic load than glucose, it has numerous unpleasant effects on health status [48]. Diets containing large amounts of fructose from sucrose (50 % fructose) or HFCS (42–55 % fructose) has been associated with development of weight gain, visceral adiposity, dyslipidemia, insulin resistance, glucose intolerance, fatty liver and hypertension that are components of metabolic syndrome [58]. Recent findings have also reported that fructose intake may raise accumulation of visceral adiposity or ectopic fat deposition [46].

Different reviews have suggested that fructose or HFCS consumption were correlated with increased risk of obesity or metabolic syndrome [60, 63] However, others have not showed this conclusion [64, 65]. In addition to, all published meta-analyses studies have not showed a statistically significant association [66].

Clinical studies have supported that sucrose and especially fructose can stimulate weight gain and components of the metabolic syndrome. Findings showed serum triglyceride and insulin level increased in young men that consumed a diet with 200 g sucrose per day, whereas triglyceride levels did not enhanced when starch was consumed [9].

Fructose is rapidly absorbed from the diet and rapidly metabolized preferentially to lipid in the liver. Fructose can supply carbon atoms for the glycerol and the triglyceride acyl portions. Thus, fructose induces highly de novo lipogenesis, increase triglycerides levels and decrease HDL-C. High levels of fructose can serve as a relatively unregulated source of acetyl CoA. Unlike glucose, dietary fructose does not induce insulin or leptin secretion. These hormones involve in regulation of energy intake and body adiposity. In contrast, some findings have reported greater satiety and lower total energy intake after consumption of beverages contain fructose compared with glucose beverages [46].

Stimulated triglyceride synthesis by fructose lead to accumulate hepatic triglyceride, reduce hepatic insulin sensitivity, higher availability of substrate and thus increase formation of VLDL particles, increased apoB stability, and higher MTP

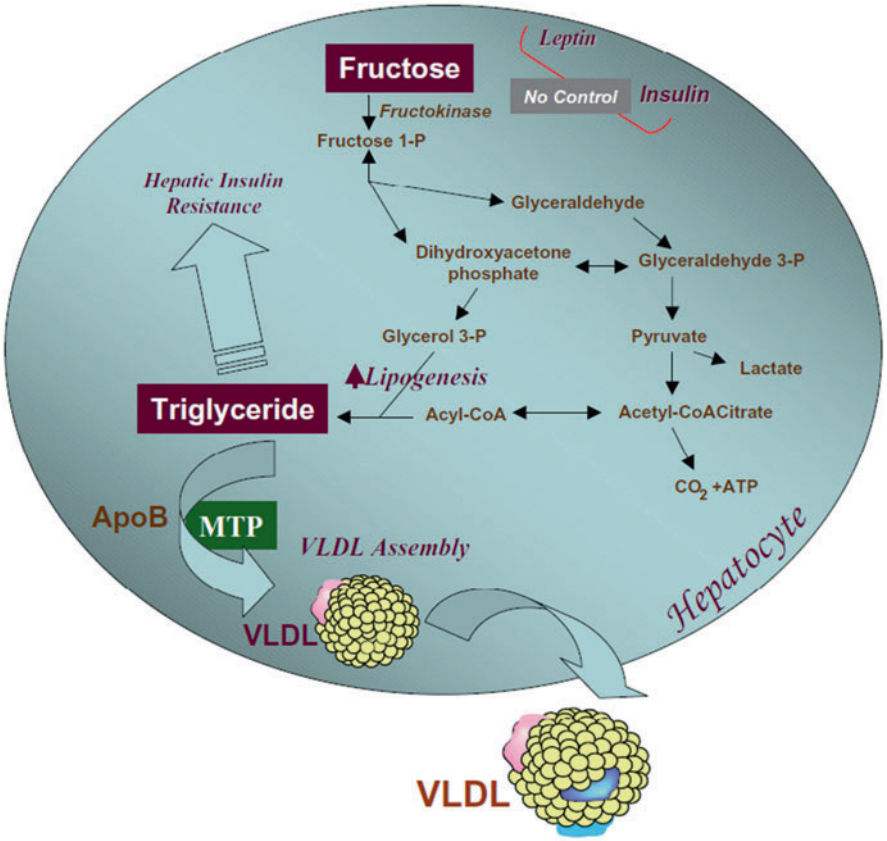

Fig. 1 Hepatic fructose metabolism: A highly lipogenic pathway [67]

(microsomal triglyceride transfer protein) (the critical factor in VLDL assembly) [22] (Fig. 1).

It has been suggested that fructose has adverse effects on blood pressure. Fructokinase phosphorylates fructose to fructose-1- phosphate. This results in a decrease in intracellular phosphate and ATP depletion, resulting in transient inhibition of protein synthesis. Adenosine monophosphate is produced and broken down by adenosine monophosphate deaminase, resulting in the generation of inosine monophosphate and eventually uric acid that it increases blood pressure. Thus, fructose consumption may stimulate hyperuricemia, and also enhance reabsorption of sodium and water; therefore the combination of sodium and fructose has a synergistic effect in e progress of hypertension [68].

In summary, according to findings, HFCS and sucrose are similar and one is not better or worse than the other. In addition to, small amounts of sugars containing fructose may be proper in diabetic patients because of the blunted glycemic response. However, they must be avoided in consumption of large amounts because

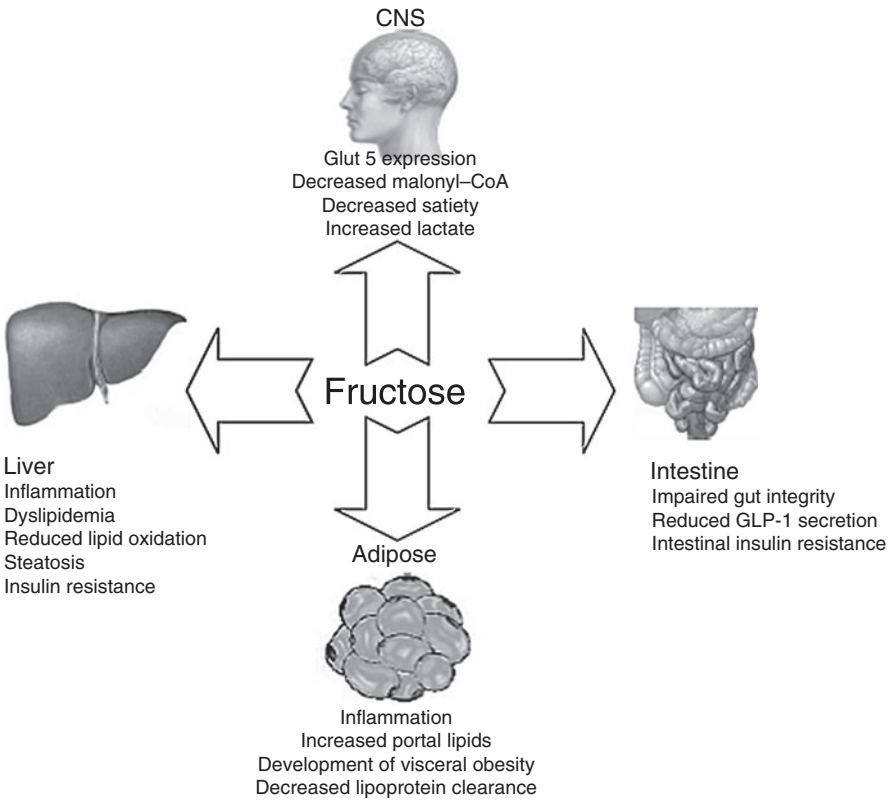

Fig. 2 Effect of fructose consumption on whole body [69]

of adverse effects on lipid profile levels; more researches are needed to identify thresholds for these effects [67]. Public notice about adverse effects of high fructose consumption on health status is so important. More efforts must be made to restrict the supplementation of foods with high fructose additives.

Chronic fructose consumption affects whole body. Multiple tissues such as liver, adipose, the gastrointestinal system and the central nervous system disturb following chronic fructose consumption. This disturbance lead to abnormalities influences including metabolic syndrome, dyslipidemia, insulin resistance and central adiposity. Impaired satiety, increased hepatic lipid deposition, inflammation and altered gastrointestinal integrity occur by fructose consumption (Fig. 2) [69].

6.1 Fructose and Uric Acid and Metabolic Syndrome

According to findings, fructose is the only sugar able to increase blood uric acid. fructokinase (also known as ketohexokinase [KHK]) phosphorylate fructose to

fructose-1-phosphate in the hepatocyte, which ATP is used as a phosphate donor. It is lead to decrease intracellular phosphate (PO4) levels and stimulate the activity of AMP deaminase 2 (AMPD2). AMP is converted to inosine monophosphate (IMP) by AMPD2. 59 nucleotidase (59NT) metabolize IMP to inosine which is further degraded to xanthine and hypoxanthine by xanthine oxidase (XO), ultimately generating uric acid. Uric acid may associate with insulin resistance in the liver by stimulating mitochondrial oxidative stress and steatosis. In addition to, uric acid blocks the ability of insulin to induce vasodilation of blood vessels, which is serious for the transfer of glucose to the skeletal muscle. Uric acid also stimulates local inflammation in the adipose tissue with decrease in the production of adiponectin. Also, uric acid has directly effects on the islet cells that cause local oxidative stress and islet dysfunction [46, 70].

According to findings, it was identified that affluent diets in sucrose can rapidly persuade features of metabolic syndrome including hyperglycemia, insulin resistance, hyperlipidemia, hypertension, weight gain, and hyperuricemia in animals. More studies indicated that these metabolic changes were due to the fructose content. In addition, if rats are pair-fed equivalent amounts of fructose or glucose with same total energy intake, only the fructose-fed rats develop features of metabolic syndrome [71, 72].

Totally, fructose lead to hypertriglyceridemia, low HDL-C, weight gain, increase blood pressure, impaired glucose tolerance, endothelial dysfunction, oxidative stress, sympathetic nervous system activation, activation of the renin angiotensin system, systemic inflammation, fatty liver, increased intra-abdominal fat accumulation, leptin resistance, proteinuria, renal hypertrophy, glomerular hypertension, and renal microvascular disease (Fig. 3) [72].

7 Summary of Proposed Mechanisms Underlying SSB and Artificial Sweeteners Adverse Metabolic Effects

Numerous possible mechanisms have been considered to link soft drink consumption with metabolic syndrome risk.

- High amounts of added sugar in soft drinks rapidly absorbed in liquid form. SSBs are consumed in large quantities that have a moderate glycemic index (GI) and high the glycemic load (GL). High GL is related to impaired glycemic control, glucose intolerance, insulin resistance and increase levels of inflammatory biomarkers such as C-reactive protein [46].
- Studies reported that high GI and GL were positively related to components of metabolic syndrome in women, but not men in Asian populations. Japanese study showed that participants that consumed the highest quartile of dietary GL had a 52 % higher risk of type II diabetes than those in the lowest quartile among women, but not men. Also, study of Koreans showed that GI and GL were positively correlated to metabolic syndrome in women but not men. In addition to, a Chinese cohort study reported that participants in the highest dietary GI and

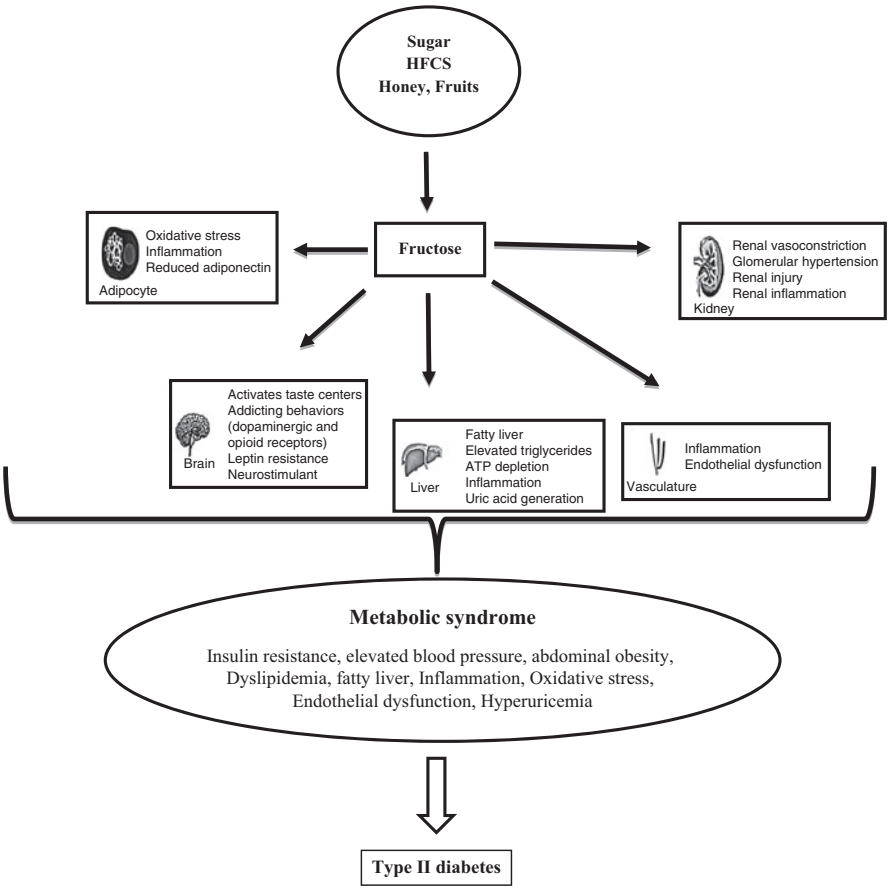

Fig. 3 Effect of sugar, HFCS, honey and fruits and finally fructose on various organ systems

GL quintiles had a 21 % and 34 % higher risk of type II diabetes, respectively. According to these findings, most of the association between dietary sugar and metabolic syndrome has been reported in women. The exact mechanisms are not understood. However some studies indicated that estrogens and androgens affect lipoprotein metabolism in opposite ways and finally cause various responses to high carbohydrate diets by gender. These different responses to high sugar consumption in Asian populations certify more investigation [44].

- SSBs increase hepatic de novo lipogenesis and finally cause hypertension and raise accumulation of visceral adipose tissue and of ectopic fat [46].
- Fructose as a major component of sugar sweetened beverages increase triglyceride levels induces insulin resistant and lead to metabolic dysfunction [73]. A high flux of fructose to the liver disturbs normal metabolism of hepatic carbohydrate. Also, disturbs glucose metabolism and glucose uptake pathways and provides

glycerol and acyl portions for increasing rate of *de novo* lipogenesis and triglyceride synthesis [67].
- Consumption of artificial sweeteners persistently can change gut microbiota that may cause metabolic abnormalities and glucose intolerance [43].
- SSBs change taste preferences and diet quality and may increase risk of disease indirectly. Persistently intake of highly sweetened beverages leads to accustomed to eating sugary foods [46].

8 Conclusions and Recommendations

There are inadequate evidence and data to determine conclusively whether NNS replace of caloric sweeteners in beverages and foods decrease added sugars or carbohydrate consumption or whether this substitution is beneficial for energy balance, body weight, cardiometabolic risk factors and metabolic disease. Limiting added sugars and monitoring carbohydrate consumption are serious strategy for keeping healthy weights and achieve glycemic control.

Some factors that may lead to the inconsistent findings about the effects of sweeteners on healthy outcome are [74]:

- Various conditions that the investigation take place
- Amount of the sweetener consumption (total and percentage of energy)
- Form and structure of the sweetener (monosaccharides, disaccharides or polysaccharides)
- The type of food in which it is present (liquid or solid)
- Presence of other saccharides and macronutrient composition in the basal diet
- Length of the study (short-term or long-term)
- Characteristics of the participants including sex, age, body size, physical activity level, energy balance status (weight gain, weight loss or weight stable)
- Health status including the presence of diabetes or metabolic syndrome
- Genetic differences among subjects.

Some findings suggested that NNS may be used to replace sources of nutritive sweetener and this replacement may reduce modestly energy intake and contribute to weight loos. Evidences showed when NNSs are consumed judiciously can promote useful effects on related metabolic parameters. However, these beneficial effects will not be fully obtained if there is a compensatory enhance in energy consumption from other sources [22].

We suggest that well-designed human trials investigating the potential role of NNS in healthy outcomes and cardiometabolic risk factors are scarce. Further researches including animal and human studies are needed to clarify the effects of different types of sweeteners on energy metabolism and chronic diseases' risk factors. However, findings of animal studies are difficult to extrapolate to humans. Many confounding variables must be considered to obtain more accurate results.

9 Cross-References

- ▶ Artificial Sweeteners
- ▶ Health Implications of Fructose Consumption in Humans
- ▶ Sugar Alcohols as Sugar Substitutes in Food Industry
- ▶ Sweeteners: Regulatory Aspects

References

1. Cummings J, Stephen A (2007) Carbohydrate terminology and classification. Eur J Clin Nutr 61 (Suppl 1):S5–S18
2. Davies G, Williams S (2016) Carbohydrate-active enzymes: sequences, shapes, contortions and cells. Biochem Soc Trans 44(1):79–87
3. Gil-Campos M, San Jose Gonzalez M, Diaz Martin J (2015) Use of sugars and sweeteners in children's diets. Recommendations of the Nutrition Committee of the Spanish Paediatric Association. An Pediatr (Barc) 83(5):353e1–353e7
4. Welsh J, Cunningham S (2011) The role of added sugars in pediatric obesity. Pediatr Clin North Am 58(6):1455–1466
5. Lustig R, Schmidt L, Brindis C (2012) Public health: the toxic truth about sugar. Nature 482 (7383):27–29
6. Duffey K, Popkin B (2008) High-fructose corn syrup: is this what's for dinner? Am J Clin Nutr 88(6):1722S–1732S
7. Karalius V, Shoham D (2013) Dietary sugar and artificial sweetener intake and chronic kidney disease: a review. Adv Chronic Kidney Dis 20(2):157–164
8. Malik V, Hu F (2012) Sweeteners and risk of obesity and type 2 diabetes: the role of sugar-sweetened beverages. Curr Diab Rep 12:195 [Epub ahead of print]
9. Johnson R, Segal M, Sautin Y, Nakagawa T, Feig D, Kang D, Gersch MS, Benner S, Sánchez-Lozada LG (2007) Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. Am J Clin Nutr 86(4):899–906
10. van Baak M, Astrup A (2009) Consumption of sugars and body weight. Obes Rev 10(Suppl 1):9–23
11. Burt B, Pai S (2001) Sugar consumption and caries risk: a systematic review. J Dent Educ 65 (10):1017–1023
12. Gross L, Li L, Ford E, Liu S (2004) Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. Am J Clin Nutr 79 (5):774–779
13. Te Morenga L, Mallard S, Mann J (2013) Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. BMJ 346:e7492
14. Coss-Bu J, Sunehag A, Haymond M (2009) Contribution of galactose and fructose to glucose homeostasis. Metabolism 58(8):1050–1058
15. American Dietetic Association (2004) Position of the American Dietetic Association: use of nutritive and nonnutritive sweeteners. J Am Diet Assoc 104(2):255–275
16. Mace O, Affleck J, Patel N, Kellett G (2007) Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. J Physiol 582(Pt 1):379–392
17. Margolskee R, Dyer J, Kokrashvili Z, Salmon K, Ilegems E, Daly K, Maillet EL, Ninomiya Y, Mosinger B, Shirazi-Beechey SP (2007) T1R3 and gustducin in gut sense sugars to regulate expression of Na + −glucose cotransporter 1. Proc Natl Acad Sci U S A 104(38):15075–15080
18. Zheng Y, Sarr M (2013) Effect of the artificial sweetener, acesulfame potassium, a sweet taste receptor agonist, on glucose uptake in small intestinal cell lines. J Gastrointest Surg 17(1):153–158

19. Araujo J, Martel F, Keating E (2014) Exposure to non-nutritive sweeteners during pregnancy and lactation: impact in programming of metabolic diseases in the progeny later in life. Reprod Toxicol 49:196–201
20. Sylvetsky A, Welsh J, Brown R, Vos M (2012) Low-calorie sweetener consumption is increasing in the United States. Am J Clin Nutr 96(3):640–646
21. Shankar P, Ahuja S, Sriram K (2013) Non-nutritive sweeteners: review and update. Nutrition 29 (11–12):1293–1299
22. Gardner C, Wylie-Rosett J, Gidding S, Steffen L, Johnson R, Reader D, Lichtenstein AH (2012) Nonnutritive sweeteners: current use and health perspectives: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 35 (8):1798–1808
23. Garcia-Almeida J, Casado Fdez G, Garcia Aleman J (2013) A current and global review of sweeteners. Regulatory aspects. Nutr Hosp 28(Suppl 4):17–31
24. Ferrer I, Thurman E (2010) Analysis of sucralose and other sweeteners in water and beverage samples by liquid chromatography/time-of-flight mass spectrometry. J Chromatogr A 1217 (25):4127–4134
25. Pepino M (2015) Metabolic effects of non-nutritive sweeteners. Physiol Behav 152 (Pt B):450–455
26. Swithers S (2015) Artificial sweeteners are not the answer to childhood obesity. Appetite 93:85–90
27. Xu H, Staszewski L, Tang H, Adler E, Zoller M, Li X (2004) Different functional roles of T1R subunits in the heteromeric taste receptors. Proc Natl Acad Sci U S A 101(39):14258–14263
28. Burke M, Small D (2015) Physiological mechanisms by which non-nutritive sweeteners may impact body weight and metabolism. Physiol Behav 152(Pt B):381–388
29. Mattes R, Popkin B (2009) Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms. Am J Clin Nutr 89(1):1–14
30. Swithers S (2013) Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements. Trends Endocrinol Metab 24(9):431–441
31. Ludwig D, Peterson K, Gortmaker S (2001) Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. Lancet 357(9255):505–508
32. Schulze M, Manson J, Ludwig D, Colditz G, Stampfer M, Willett W, Hu FB (2004) Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 292(8):927–934
33. Fernstrom J (2015) Non-nutritive sweeteners and obesity. Annu Rev Food Sci Technol 6:119–136
34. Fowler S, Williams K, Resendez R, Hunt K, Hazuda H, Stern M (2008) Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. Obesity 16 (8):1894–1900
35. Renwick A, Molinary S (2010) Sweet-taste receptors, low-energy sweeteners, glucose absorption and insulin release. Br J Nutr 104(10):1415–1420
36. Swithers S, Sample C, Davidson T (2013) Adverse effects of high-intensity sweeteners on energy intake and weight control in male and obesity-prone female rats. Behav Neurosci 127 (2):262–274
37. Swithers S, Laboy A, Clark K, Cooper S, Davidson T (2012) Experience with the high-intensity sweetener saccharin impairs glucose homeostasis and GLP-1 release in rats. Behav Brain Res 233(1):1–14
38. Mitsutomi K, Masaki T, Shimasaki T, Gotoh K, Chiba S, Kakuma T, Shibata H (2014) Effects of a nonnutritive sweetener on body adiposity and energy metabolism in mice with diet-induced obesity. Metabolism 63(1):69–78
39. Moran A, Al-Rammahi M, Zhang C, Bravo D, Calsamiglia S, Shirazi-Beechey S (2014) Sweet taste receptor expression in ruminant intestine and its activation by artificial sweeteners to regulate glucose absorption. J Dairy Sci 97(8):4955–4972

40. Sivertsen J, Rosenmeier J, Holst J, Vilsboll T (2012) The effect of glucagon-like peptide 1 on cardiovascular risk. Nat Rev Cardiol 9(4):209–222
41. Abou-Donia M, El-Masry E, Abdel-Rahman A, McLendon R, Schiffman S (2008) Splenda alters gut microflora and increases intestinal p-glycoprotein and cytochrome p-450 in male rats. J Toxicol Environ Health A 71(21):1415–1429
42. Larsen N, Vogensen F, van den Berg F, Nielsen D, Andreasen A, Pedersen B, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M (2010) Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One 5(2):e9085
43. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss C, Maza O, Israeli D, Zmora N, Gilad S, Weinberger A, Kuperman Y, Harmelin A, Kolodkin-Gal I, Shapiro H, Halpern Z, Segal E, Elinav E (2014) Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 514(7521):181–186
44. Chung S, Ha K, Lee H, Kim C, Joung H, Paik H, Song Y (2015) Soft drink consumption is positively associated with metabolic syndrome risk factors only in Korean women: data from the 2007–2011 Korea National Health and Nutrition Examination Survey. Metabolism 64 (11):1477–1484
45. Kumar G, Pan L, Park S, Lee-Kwan S, Onufrak S, Blanck H (2014) Sugar-sweetened beverage consumption among adults – 18 states, 2012. Morb Mortal Wkly Rep 63(32):686–690
46. Malik V, Popkin B, Bray G, Despres J, Willett W, Hu F (2010) Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care 33 (11):2477–2483
47. Malik V, Pan A, Willett W, Hu F (2013) Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. Am J Clin Nutr 98(4):1084–1102
48. Huang C, Huang J, Tian Y, Yang X, Gu D (2014) Sugar sweetened beverages consumption and risk of coronary heart disease: a meta-analysis of prospective studies. Atherosclerosis 234 (1):11–16
49. Hu F (2013) Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. Obes Rev 14(8):606–619
50. Swithers S, Martin A, Davidson T (2010) High-intensity sweeteners and energy balance. Physiol Behav 100(1):55–62
51. Miller P, Perez V (2014) Low-calorie sweeteners and body weight and composition: a meta-analysis of randomized controlled trials and prospective cohort studies. Am J Clin Nutr 100 (3):765–777
52. Malik A, Akram Y, Shetty S, Malik S, Yanchou Njike V (2014) Impact of sugar-sweetened beverages on blood pressure. Am J Cardiol 113(9):1574–1580
53. Jayalath V, Sievenpiper J, de Souza R, Ha V, Mirrahimi A, Santaren I, Blanco Mejia S, Di Buono M, Jenkins AL, Leiter LA, Wolever TM, Beyene J, Kendall CW, Jenkins DJ (2014) Total fructose intake and risk of hypertension: a systematic review and meta-analysis of prospective cohorts. J Am Coll Nutr 33(4):328–339
54. Nguyen S, Choi H, Lustig R, Hsu C (2009) Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. J Pediatr 154(6):807–813
55. Kim Y, Abris G, Sung M, Lee J (2012) Consumption of sugar-sweetened beverages and blood pressure in the United States: the national health and nutrition examination survey 2003–2006. Clin Nutr Res 1(1):85–93
56. Brown I, Stamler J, Van Horn L, Robertson C, Chan Q, Dyer A, Huang CC, Rodriguez BL, Zhao L, Daviglus ML, Ueshima H, Elliott P (2011) Sugar-sweetened beverage, sugar intake of individuals, and their blood pressure: international study of macro/micronutrients and blood pressure. Hypertension 57(4):695–701
57. Greenwood D, Threapleton D, Evans C, Cleghorn C, Nykjaer C, Woodhead C, Burley VJ (2014) Association between sugar-sweetened and artificially sweetened soft drinks and type 2 diabetes: systematic review and dose–response meta-analysis of prospective studies. Br J Nutr 112(5):725–734

58. Rabie E, Heeba G, Abouzied M, Khalifa M (2015) Comparative effects of Aliskiren and Telmisartan in high fructose diet-induced metabolic syndrome in rats. Eur J Pharmacol 760:145–153
59. Dhingra R, Sullivan L, Jacques P, Wang T, Fox C, Meigs J, D'Agostino RB, Gaziano JM, Vasan RS (2007) Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. Circulation 116(5):480–488
60. Hu F, Malik V (2010) Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence. Physiol Behav 100(1):47–54
61. Chan T, Lin W, Huang H, Lee C, Wu P, Chiu Y, Huang CC, Tsai S, Lin CL, Lee CH (2014) Consumption of sugar-sweetened beverages is associated with components of the metabolic syndrome in adolescents. Nutrients 6(5):2088–2103
62. Baik I, Lee M, Jun N, Lee J, Shin C (2013) A healthy dietary pattern consisting of a variety of food choices is inversely associated with the development of metabolic syndrome. Nutr Res Pract 7(3):233–241
63. Stanhope K, Havel P (2010) Fructose consumption: recent results and their potential implications. Ann N Y Acad Sci 1190:15–24
64. Dolan L, Potter S, Burdock G (2010) Evidence-based review on the effect of normal dietary consumption of fructose on development of hyperlipidemia and obesity in healthy, normal weight individuals. Crit Rev Food Sci Nutr 50(1):53–84
65. Tappy L, Le K, Tran C, Paquot N (2010) Fructose and metabolic diseases: new findings, new questions. Nutrition 26(11–12):1044–1049
66. Khitan Z, Kim D (2013) Fructose: a key factor in the development of metabolic syndrome and hypertension. J Nutr Metab 2013:682673
67. Basciano H, Federico L, Adeli K (2005) Fructose, insulin resistance, and metabolic dyslipidemia. Nutr Metab (Lond) 2(1):5
68. Sayon-Orea C, Martinez-Gonzalez M, Gea A, Alonso A, Pimenta A, Bes-Rastrollo M (2015) Baseline consumption and changes in sugar-sweetened beverage consumption and the incidence of hypertension: the SUN project. Clin Nutr 34(6):1133–1140
69. Dekker M, Su Q, Baker C, Rutledge A, Adeli K (2010) Fructose: a highly lipogenic nutrient implicated in insulin resistance, hepatic steatosis, and the metabolic syndrome. Am J Physiol Endocrinol Metab 299(5):E685–E694
70. Johnson R, Nakagawa T, Sanchez-Lozada L, Shafiu M, Sundaram S, Le M, Ishimoto T, Sautin YY, Lanaspa MA (2013) Sugar, uric acid, and the etiology of diabetes and obesity. Diabetes 62 (10):3307–3315
71. Reungjui S, Roncal CA, Mu W, Srinivas TR, Sirivongs D, Johnson RJ, Nakagawa T (2007) Thiazide diuretics exacerbate fructose-induced metabolic syndrome. J Am Soc Nephrol 18:2724–2731
72. Johnson RJ, Perez-Pozo SE, Sautin YY, Manitius J, Sanchez-Lozada LG, Feig DI et al (2009) Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes. Endocr Rev 30 (1):96–116
73. Bray G (2012) Fructose and risk of cardiometabolic disease. Curr Atheroscler Rep 14 (6):570–578
74. Murphy S (2009) The state of the science on dietary sweeteners containing fructose: summary and issues to be resolved. J Nutr 139(6):1269S–1270S