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ORIGINAL ARTICLE

Sugary drinks in the pathogenesis of obesity and cardiovascular diseases

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Soft drink overconsumption is now considered to be a major public health concern with implications for cardiovascular diseases. This follows a number of studies performed in animals suggesting that chronic consumption of refined sugars can contribute to metabolic and cardiovascular dysregulation. In particular, the monosaccharide fructose has been attracting increasing attention as the more harmful sugar component in terms of weight gain and metabolic disturbances. High-fructose corn syrup is gradually replacing sucrose as the main sweetener in soft drinks and has been blamed as a potential contributor to the current high prevalence of obesity. There is also considerable evidence that fructose, rather than glucose, is the more damaging sugar component in terms of cardiovascular risk. This review focuses on the potential role of sugar drinks, particularly the fructose component, in the pathogenesis of obesity and cardiovascular diseases.
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Trends in consumption of sugary drinks

According to the data from the Economic Research Service of the US Department of Agriculture,[1] the average American consumed 64 kg of added sugars in 2005.[1] Soft drinks contribute about a third of the total daily sugar intake, making them the main source of added sugar in the diet.[2] Of particular concern is the rising consumption of soft drinks among young people. Between 1977–1978 and 1994–1996 the proportion of daily energy intake contributed by soft drinks increased by more than 80% in children and adolescents aged between 2 and 18 years.[3] A recent cross-sectional study in children and adolescents revealed that there is a link between salt intake and consumption of fluids, including soft drinks.[4] Easy access to soft drinks in school cafeterias and vending machines as well as aggressive advertising strategies targeted toward young people are likely to have contributed to the high rates of soft drink consumption among children and teenagers.[5,6] The sugar content of soft drinks is typically 10–15 g per 100 ml. In the United States over the last three decades, high-fructose corn syrup (HFCS) has largely replaced sucrose as the major sweetener in soft drinks.[7] HFCS is manufactured by an industrial process by which corn starch is initially converted to glucose, which then undergoes isomerization to fructose. HFCS is produced in two forms, both of which comprise fructose and glucose: HFCS-42 (42% fructose) and HFCS-55 (55% fructose). Compared with sucrose, HFCS is cheaper to produce and is therefore an attractive choice of sweetener from a commercial point of view. Although most HFCS in the diet is consumed in the form of soft drinks, other sweetened processed foods such as cakes, canned fruits, sweets and even bread may also contain HFCS.

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Do soft drinks contribute to weight gain?

In a review article published in 2004, Bray *et al.*[7] argued that the consumption of beverages containing HFCS has directly contributed to the obesity epidemic. This hypothesis was based on the observation that the increase in consumption of free fructose (particularly as HFCS) and the rise in the prevalence of obesity have followed similar time courses over the last 30 years. The idea that there is a direct association between fructose consumption and the obesity epidemic is, however, controversial because parallel time courses and correlations between two phenomena are not an adequate basis for establishing a cause–effect relationship. Nevertheless, the high contribution of soft drink consumption to overall energy intake is still likely to be a factor causing weight gain. Indeed, a number of studies have attempted to determine the importance of soft drink consumption as a

contributor to weight gain and obesity. Malik *et al*.[8] noted that results from several large scale cross-sectional investigations, including studies in children or adolescents, showed that on balance, there is a positive association between consumption of sugar-sweetened beverages and overweight or obesity.[9–12] A potential problem with cross-sectional studies, however, is the difficulty in controlling for other lifestyle factors that are also conducive to obesity. For example, levels of soft drink consumption are correlated with low socioeconomic status, poor diet, physical inactivity and even smoking.[8] Furthermore, overweight individuals selected for such a study might be actively trying to lose weight at the time of being questioned and could, therefore, either be currently restricting their soft drink intake or even underreporting their actual consumption of soft drinks. For these reasons, carefully controlled dietary intervention studies are probably of more value in determining the potential contribution of sugar-sweetened beverages to weight gain. In this context, individuals whose regular diet was supplemented with either sucrose or HFCS were found to have increased body weight and fat mass compared with individuals whose diets were supplemented with artificial sweeteners.[13,14] Another intervention study reported that restriction of soft drink consumption in a group of adolescents resulted in a decrease in body weight.[15] These studies seem to support the concept that the extent of consumption of sugar in the form of soft drinks can influence the gain or loss of body weight.

The most obvious mechanism by which soft drinks can increase body weight is by the increase in overall energy intake due to consumption of soft drinks on top of a regular diet. In general, liquid meals are less satiating than solid foods, thereby promoting elevated energy intake.[16] Furthermore, energy obtained from soft drinks is not completely compensated for by a reduction in energy intake from other foods.[14,17]

Fructose consumption promotes adiposity

Consumption of refined sugar, particularly the fructose component, has been postulated to promote adiposity and weight gain. Once ingested, the metabolism of fructose differs from that of glucose. Fructose is phosphorylated in the liver to fructose-1-phosphate by fructokinase and can then be converted to glycerol-3-phosphate, which is the basis for triacylglycerol synthesis.[18] Unlike glucose, fructose metabolism bypasses phosphofructokinase, which is an important rate-limiting step in glycolysis.[18] Therefore, when fructose is consumed in high amounts the production of glycerol-3-phosphate as a substrate for triacylglycerol synthesis proceeds unchecked. As such, acute ingestion of fructose leads to substantially increased triacylglycerol levels in humans[19,20] and animals.[21,22] In a chronic study in mice, the effects of *ad libitum* access to drinks containing fructose, sucrose and water on body weight, adiposity and energy metabolism were compared.[23] Not only did the fructose-drinking mice have the greatest increases in body weight, but also in body fat when expressed both in absolute and percentage terms, even though total calorie intake (food and beverages) did not differ between the groups.[22] In humans, there are very few studies on the effects of fructose on adiposity or weight gain. It was, however, reported that supplementation of the daily diet with 50–60 g fructose in diabetic individuals over a period of 23 weeks led to increased weight gain that could be attributed to an overall increase in energy intake.[24]

Fructose and insulin resistance

Studies in rodents have shown that diets that are high in fructose are not only associated with raised triglycerides and adiposity but also with the onset of insulin resistance.[22,25,26] The precise mechanisms of the links between fructose consumption, hypertriglyceridemia and insulin resistance remain to be established but might be related to intracellular accumulation of lipids.[18] In young healthy humans, a 25% reduction in insulin sensitivity has been documented after a 2-week high-sucrose diet.[27] The fructose component is probably responsible for the onset of insulin resistance because supplementing a regular diet with 250 g fructose per day caused a significant reduction in insulin sensitivity in as little as 7 days, whereas the same amount of glucose had no effect.[28] More recent studies reported that a high-fructose diet (3 g per kg body weight per day) led to dyslipidemia and hepatic insulin resistance.[29] But further studies by the same group showed that dietary supplementation with a lower dose of fructose (1.5 g per kg body weight per day) did not invoke insulin resistance.[30] The effects of fructose diets on insulin sensitivity in humans therefore seem to be dose dependent. It remains to be seen, however, whether consumption of fructose in amounts comparable with those obtained from regular consumption of soft drinks might have deleterious effects on insulin sensitivity in humans.

Refined sugar and cardiovascular diseases

Animal studies have shown strong associations between high refined-sugar intake and the onset of arterial hypertension. Rats who had their drinking water replaced with an 8% sucrose solution developed hypertension and tachycardia that was evident within a week and was not related to weight gain.[31] Sucrose-fed rats were found to have increased norepinephrine turnover in their hearts,[32] pancreas and liver,[33] suggesting enhanced sympathetic activation in these organs. Several reports suggest that chronic fructose feeding may lead to hypertension in rats [34–37] and dogs,[22] and to nocturnal hypertension in mice.[38] However, other studies, using 24-h recordings rather than tail cuff techniques to

measure blood pressure, reported that fructose feeding did not cause hypertension in rats or dogs.[39,40] In rats, high-fructose diets have been shown to induce left ventricular hypertrophy[41,42] that seems to be related to activation of the renin–angiotensin system and stimulation of sympathetic activity.[41] Fructose consumption has also been linked to the development of glomerular hypertension[43] and chronic renal disease[44] in rats.

In contrast to a high-fructose diet, a diet that is high in glucose does not lead to hypertension, elevated plasma triglycerides, insulin resistance or hyperinsulinemia.[22] It therefore seems that fructose is the more damaging sugar component in terms of cardiovascular risk. The mechanisms that link fructose intake with the onset of hypertension are poorly understood. Insulin resistance and hyperinsulinemia are both associated with elevated sympathetic activity and the subsequent onset of hypertension.[45,46] Other factors such as vascular endothelial dysfunction induced by fructose might also play a role.[37,47]

Uric acid—a link between fructose and cardiovascular diseases?

A potential mechanism linking fructose consumption with the long-term development of metabolic syndrome and cardiovascular diseases is uric acid. Ingesting fructose rapidly elevates uric acid concentrations[48] via a process that is related to the metabolism of fructose within hepatocytes. Fructose is phosphorylated to fructose-1-phosphate by fructokinase in a reaction that requires the donation of phosphate from ATP. Because the phosphorylation of fructose is unregulated, intracellular ATP depletion occurs, leading to the generation of ADP and subsequent degradation to uric acid.[49] It has long been recognized that hyperuricemia is a predictor for elevated cardiovascular risk. Specifically, studies have shown strong associations between elevated serum uric acid levels and development of hypertension,[50] as well as mortality from cardiovascular diseases.[51] Uric acid is also an independent risk factor for type 2 diabetes in humans.[52] There is experimental evidence that hyperuricemia plays a key role in the development of fructose-induced metabolic syndrome. In fructose-fed rats, administration of allopurinol, a drug that blocks uric acid production, improved several markers of metabolic syndrome, namely blood pressure, insulin levels and plasma triglycerides.[53] Thus, uric acid may be a pivotal link between high-fructose diets and the development of metabolic syndrome and subsequent increased cardiovascular risk.

Chronic studies in humans

Only a few epidemiological studies in humans have addressed the long-term health impact of high-sugar diets. Early studies performed in the 1960s and 1970s by Yudkin *et al.*[54,55] demonstrated that a high sugar intake was associated with cardiovascular disease. A later study in 75 000 women showed a positive association between diets that are high in refined carbohydrate and the incidence of coronary heart disease.[56] A more recent study published in 2007 showed that middle-aged individuals consuming more than one soft drink daily had a 48% higher prevalence of metabolic syndrome than those who consumed less than one soft drink per day.[57] In overweight schoolchildren, consumption of free fructose was found to be a predictor of smaller low-density lipoprotein size,[58] which represents a risk factor for metabolic syndrome.[59,60] Thus, dietary intake of fructose, even at a young age, may be setting the scene for the later development of cardiometabolic disease.

Acute effects of soft drinks in humans

Acute physiological changes in the postprandial state may contribute, over the long term, to the development of cardiovascular diseases.[61] In particular, meals that are high in lipids and sugars can lead to a state of 'postprandial dysmetabolism' that is characterized by oxidative stress, endothelial dysfunction and elevated sympathetic activity.[62] Considering the potential link between high-sugar diets and hypertension from animal studies, it is rather surprising that the mechanisms of the acute responses to ingesting soft drinks have not yet been comprehensively studied in humans. Because humans spend much of their time in a postprandial state, even acute effects, if repeated often enough, could lead to cumulative adverse effects.

Several studies in humans have determined the acute effects of glucose and fructose intake on sympathetic activity and regional blood flow. Although both glucose and fructose result in cardiac sympathetic activation with a subsequent increase in heart rate,[63–65] there are important differences between these monosaccharides regarding their effects on vascular tone. Whereas glucose infusion augments muscle nerve sympathetic activity and causes vasodilatation in skeletal muscle, infusion of fructose does not.[66] The contrasting vascular responses to fructose and glucose might be explained by the hemodynamic actions of insulin, which causes vasodilatation in the skeletal muscle.[67] Compared with glucose, acute ingestion of fructose has a negligible effect on secretion of insulin.[68,69] The elevated cardiac output after fructose ingestion, combined with a lack of insulin-mediated peripheral vasodilatation, therefore has the potential to acutely raise blood pressure. In a randomized crossover trial we compared the acute effects of ingesting glucose and fructose in healthy young volunteers.[70] We found that ingesting a 500 ml drink containing 60 g fructose significantly increased blood pressure for at least 2 h after the drink (Figure 1). The blood pressure elevation in response to fructose was characterized by cardiac sympathetic activation

with an increase in cardiac output but no change in total peripheral resistance. Ingesting a drink containing the same amount of glucose also increased cardiac output but with a concomitant peripheral vasodilatation; thus, there was no net change in blood pressure. Although it is difficult to extrapolate acute responses to long-term effects, it is possible that diets that include repeated fructose loads might contribute, over time, to increased cardiovascular risk.

Potential interactions of soft drinks with fast food

Soft drinks are not only consumed in isolation but often as part of a meal. In particular, soft drinks are consumed in large quantities at fast food restaurants,[71] frequently together with high-fat meals. Ingestion of a high-fat meal increases blood triglyceride levels resulting in endothelial dysfunction for several hours after the meal.[72] Because ingestion of a fructose drink enhances the postprandial increase in plasma triglycerides seen after an oral fat load,[73] a fast food meal that is high in fat and sugar has the potential to further attenuate postprandial endothelial function, possibly leading over time to increased cardiovascular risk.

The role of caffeine in soft drinks

Caffeine is a constituent of many soft drinks, with concentrations ranging from about 10 to 15 mg per 100 ml. Soft drinks are the second largest contributor to total caffeine intake, and are the primary source of caffeine for children and teenagers.[74] The caffeine content of soft drinks is much lower than the dosages that have been shown to acutely elevate blood pressure. Nevertheless, one study of 155 000 women suggested that caffeine consumption in the form of soft drinks was more likely to be associated with hypertension than caffeine consumed as coffee.[75] In metabolic studies, doses of caffeine that, when administered alone, are too low to stimulate thermogenesis can potentiate the thermogenic effects of sympathetic stimulation induced by

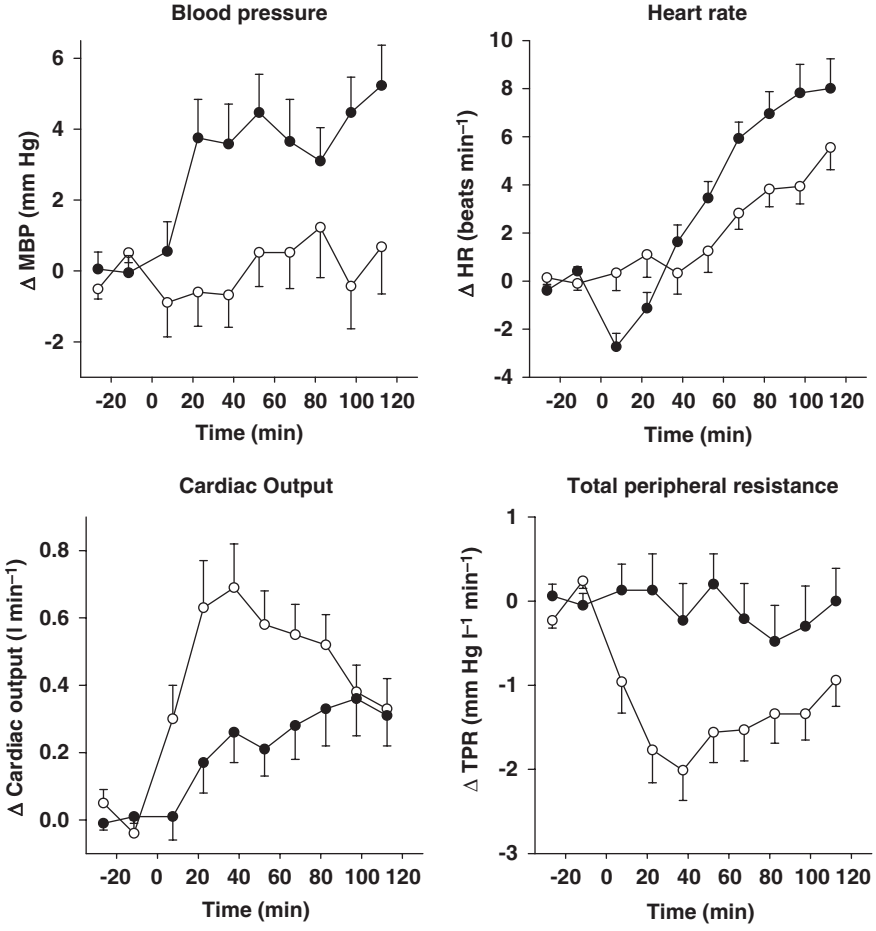

Figure 1 Time course of the changes in mean blood pressure (MBP), heart rate (HR), cardiac output and total peripheral resistance (TPR) in response to ingesting drinks containing glucose (○) and fructose (●). The drinks were ingested at time 0 min. Adapted with permission from Brown *et al*.[70]

other substances.[76] Caffeine added to soft drinks might therefore have the potential to modify the autonomic responses to ingestion of sugar, resulting in an acute cardiovascular dysregulation.

A relatively recent phenomenon is the upsurge in popularity of so-called 'Energy Drinks'—a category of soft drinks that are marketed for their stimulatory properties. These stimulatory effects of energy drinks can be largely attributed to caffeine, which is present in much higher concentrations (typically 32 mg per 100 ml) than in regular soft drinks. Concerns about the safety of energy drinks have led the European Union to warrant that energy drinks carry a health warning and some countries restrict or prohibit their sale. As yet, however, there is very little scientific information about the potential health risks associated with energy drinks.

Is high-fructose corn syrup really a major problem?

The increasing use of HFCS at the expense of sucrose as a sweetener in soft drinks has attracted considerable negative publicity. But is HFCS really worse than sucrose? Fructose intake from soft drinks is actually very similar whether HFCS (55% fructose) or sucrose (50% fructose) is used as the sweetener in soft drinks. Bray *et al*.[7] attributed free fructose (as a component of HFCS), rather than bound fructose (as a component of sucrose), as a major contributor to the obesity epidemic. There is, however, no evidence that prevalence of obesity or overweight would be any less had sucrose not largely been replaced by HFCS as the sweetener of choice in soft drinks.

Only a small number of studies have compared the effects of sucrose with HFCS. One study showed that the short-term metabolic responses to a beverage sweetened with HFCS are no different to one sweetened with sucrose.[77] Another study showed that drinks that were sweetened with either sucrose or HFCS did not have significantly different effects on hunger, satiety or on energy intake at a subsequent lunch.[78] In the absence of long term studies on the effects of HFCS versus sucrose, it seems premature to blame the switch to HFCS as a major contributor to the pathogenesis of obesity or cardiovascular diseases.

Conclusion

There is overwhelming evidence from both animal and human studies that fructose may have a key role in elevating metabolic and cardiovascular risk factors. There is a clear need for human studies to determine the cardiovascular effects of soft drinks when consumed on a more chronic basis. Furthermore, mechanisms of cardiovascular dysregulation induced by fructose and the potential interactions with other dietary nutrients need to be elucidated.

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Conflict of interest

The authors have declared no financial interests.

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