

MINI-REVIEW

The Fructose mystery: How bad or good is it?

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Abstract: This review article endeavoured to ascertain the facts about fructose, a mono-saccharide sugar being increasingly used in daily diet. Human and animal studies suggest that fructose ingestion produces deleterious effects on the cardiovascular system, such as increase in blood pressure and also has adverse metabolic effects, for example insulin resistance and hypertriglyceridaemia. On the other hand it has also been determined that fructose, especially that is contained in natural sources as apples, dates and honey may produce beneficial effects on human health; smaller amounts of fructose may even help improve diabetic control and that adequate seminal fructose concentrations help promote male fertility. In conclusion, fructose appears to be not all that bad; is essential for male fertility, small amounts of fructose, specifically which comes from dietary sources appears to be beneficial for health.

Keywords: Fructose, fertility, honey, cardiovascular system, blood pressure, monosaccharides.

INTRODUCTION

Economic progression leads to changes in life style and dietary habits consistent with modern living. Sugars, i.e., mono- and disaccharides, such as glucose, sucrose and lactose are used in various dietary items, with fructose use in human diet increasing several folds in the past 50 years. Fructose occupies about 8% of every day energy intake by food articles, for example, fruit or fruit products, bakery related items and soft beverages (Park & Yetley, 1993a). There has been a rising utilization of fructose particularly in beverages that have become almost an essential part of the daily diet (Park & Yetley, 1993b; Bray *et al.*, 2004). Fructose, as compared to glucose, has negligible effects on insulin secretion and does not raise blood glucose level; smaller amounts may even reduce blood glucose (Moore *et al.*, 2000) but its utilization is connected with adverse cardiovascular (CV) effects and grave metabolic complications particularly in overweight and obese people (Stanhope *et al.*, 2009).

Cardiovascular and metabolic effects

Excessive and long-term use of fructose, especially in food items containing high-fructose corn syrup, may result in insulin resistance (IR), hypertension, and hypertriglyceridaemia (Hwang *et al.*, 1987b; Stanhope *et al.*, 2008). Evidence suggested that male rats fed on fructose rich diet developed hyperinsulinaemia, IR and increase in systolic blood pressure (SBP) (Hwang *et al.*, 1987a) while female rats did not show these effects probably because of female sex hormones (Hwang *et al.*, 1987a; Galipeau *et al.*, 2002). Animal studies further suggested that in rats who were fed a fructose rich diet

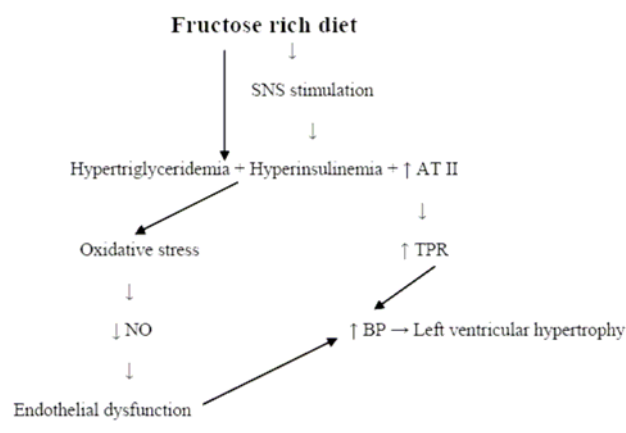
there was an increase in left ventricular weight. It has been proposed that fructose enriched diet leads to a rise in serum insulin and angiotensin II (AT II) levels with consequent elevation of total peripheral resistance (TPR) and blood pressure (BP) resulting in left ventricular hypertrophy (Kobayashi *et al.*, 1993a) and that angiotensin increased oxidative stress, impairing endothelium-dependant vasodilatation (Dijkhorst-Oei *et al.*, 1999; Higashi *et al.*, 2002b). Animal studies suggested that fructose-induced hyperinsulinaemia, an outcome of stimulation of the sympathetic nervous system (SNS) (Verma *et al.*, 1999) and hypertriglyceridemia (Sleder *et al.*, 1980) resulted in the production of superoxide radicals and contributed to oxidative stress, reducing the amount of nitric oxide (NO) in the vasculature leading to altered vascular function and defective vasodilatation (Higashi *et al.*, 2002a; Hsieh, 2004; Oudot *et al.*, 2008).

Proposed mechanisms of rise in BP and endothelial dysfunction in fructose fed rats.

Diets rich in carbohydrates especially that containing high fructose and sucrose (a disaccharide made up of fructose and glucose) produce potentially adverse effects on the serum triacylglycerol (TG) level, i.e., have a propensity to increase it. There are specific enzymes for the phosphorylation of fructose which then either enters the glycolytic pathway and feeds into the citric acid cycle or enters gluconeogenesis to be converted to glucose and stored as glycogen (Tappy *et al.*, 1986; Segal *et al.*, 2007). As fructose is consumed and absorbs it gets converted to fructose-1- phosphate by the action of fructokinase in the liver and then to glycerol-3- phosphate which becomes backbone for TG synthesis (Frayn & Kingman,

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1995), while HDL concentration decline, which predisposes to cardiovascular disease (CVD) (Parks & Hellerstein, 2000; Fried & Rao, 2003b). Thus, fructose rich diets raise serum TG concentrations. However, such increase was reported to be evident in males but in women no similar change was apparent (Bantle *et al.*, 2000; Couchepin *et al.*, 2008), presumably because of female sex hormones (Macdonald, 1966).



Fructose and increase in BP

A study used fructose and glucose containing drinks to produce an acute load of these sugars and compared it with water as a control drink. Brown *et al.* (2008) reported a rise in systolic and diastolic BP after ingestion of fructose containing drink in healthy human volunteers. The magnitude of the pressor response was 6.2 ± 0.8 mmHg above the baseline SBP. In addition, fructose ingestion significantly raised heart rate and cardiac output (CO), while TPR remained unchanged. This study also demonstrated a rise in respiratory quotient and increased oxygen consumption with fructose and glucose drinks (Brown *et al.*, 2008). A possible physiological explanation for these findings could be the SNS stimulation after glucose and fructose consumption; as it is known that insulin secretion leads to SNS stimulation (Rowe *et al.*, 1981) and increased thermogenesis (increased energy expenditure subsequent to nutrient ingestion) after fructose intake points to such activity. In a recent study by Memon *et al.* (2011) it was confirmed that acute consumption of fructose increased SBP and DBP in humans (Memon *et al.*, 2011). However, Brown *et al.* (2008) reported an increase in CO after fructose ingestion, whereas Brundin and Wahren (1993) reported unchanged CO in healthy, male subjects, 60 min post- fructose consumption (Brundin & Wahren, 1993).

A number of factors may be involved that help promote BP rise after fructose consumption. Rats showed an increase in AT II levels but not BP after they were fed with fructose chronically (Kobayashi *et al.*, 1993) while mice had an increase in AT II and SBP (Farah *et al.*, 2006). In the latter study, increase in BP was related with enhanced sympathetic activity but without change in

baroreflex sensitivity (BRS). Brown *et al.* (2008) on the other hand, reported an increase in BP and augmented cardiac sympathetic activity along with attenuated BRS after acute fructose consumption in human volunteers (Brown *et al.*, 2008). It has also been suggested that rats who were fed a fructose enriched diet developed endothelial dysfunction, as a result of production of free radicals (Oudot *et al.*, 2008) and attenuated release of NO (Hsieh, 2004). The deficient insulin release in response to fructose (Pozza *et al.*, 1958) and the consequent absence of vasodilator role of insulin may also contribute to increase BP after fructose ingestion. Evidence suggest that thermogenesis is higher with fructose than with equivalent load of glucose (Tappy *et al.*, 1986) and since adaptive thermogenesis, non-shivering and dietary, is regulated by the SNS (Landsberg & Young, 1984; Reaven *et al.*, 1996) it is likely that the SNS is stimulated due to fructose consumption, as it has been reported that sympathectomy prevented development of hypertension in rats fed on fructose (Verma *et al.*, 1999).

Fructose and fertility

Effects produced by fructose consumption on human health remain controversial; we know since long that fructose content of human semen plays an important role in fertility; values below normal range, i.e., less than 1200 $\mu\text{g} / \text{ml}$ in the seminal fluid leads to infertility, and that increasing seminal fructose level by administering androgens would result in achieving fertility (Schirren, 1963). Asthenozoospermia, i.e., reduced sperm motility; one of the causes of infertility, improved after treatment if true corrected seminal fructose increased (Gonzales & Villena, 2001).

Fructose, lipids and diabetes type –II

Evidence suggests that if total carbohydrate is increased but fructose content is held at 18-20 g / day, fasting serum TG levels do not change (Vidon *et al.*, 2001). It has also been reported that a small dose (7.5/g) of fructose improved oral glucose tolerance in adults suffering from diabetes type –II (Moore *et al.*, 2001) implying that small amounts of fructose do not produce harmful effects. Short-term dose response studies show that with sucrose providing $\leq 18\%$ of energy in a high carbohydrate diet, there will be no deleterious effect or change in serum TG level whereas addition of fibre to the diet attenuates the effects of a high sucrose diet on serum TG levels (Albrink & Ullrich, 1986). This indicates that a diet rich in carbohydrate, but with the concentration of sucrose and fructose kept in the recommended range, would have no effect on serum TG levels as the CVD risk is ‘dose dependent’ for these sugars (Fried & Rao, 2003). Hallfrisch (1990) reviewed various studies and in a number of studies it was reported that cholesterol did not increase after fructose consumption (Hallfrisch, 1990). It has also been reported that there were no adverse effects on lipid metabolism and glycemic control of moderate

amounts of fructose added to physiologic mixed diets in obese ambulatory patients with diabetes type-II, rather an improvement in glycemic control would reduce risk for coronary artery disease (CAD) (Osei *et al.*, 1987).

Fructose from natural sources

Apple

It has also been reported that fructose ingestion (64 g, i.e., equivalent to that contained in the mass of 5 apples) may produce beneficial effects by increasing plasma anti-oxidant levels in humans (Lotito & Frei, 2004). Animal study conducted on mice has reported a very low effect of apple-extracted fructose, used acutely, on glycemic and insulin response as compared to other sugars, whereas its long-term exposure improved glucose tolerance without modifying food intake and body weight (Dray *et al.*, 2009).

Honey

Fructose is present (42.4% of weight) in honey (Hallfrisch, 1990); evidence suggests that the fructose moiety of honey exerts a hypoglycemic effect by increasing hepatic glucose uptake, glycogen synthesis and its deposition (Erejuwa *et al.*, 2012).

Dates

Dates are yet another dietary source rich in fructose (Al-Farsi & Lee, 2008) but cannot be ascribed as potentially detrimental to health, as they are considered to provide health benefits (Vayalil, 2012). Dates along with fructose also contain antioxidants (Al-Farsi & Lee, 2008) which may neutralize oxidant stress produced by fructose. It was further determined that a negative co-relation existed between fructose portion and the glycemic index value of the dates (Ali *et al.*, 2009). Presence of fibre in the fruit sources of fructose e.g., apple, banana and dates (USDA National Nutrient Database for Standard Reference) may further help attenuate any adverse fructose effects (Albrink & Ullrich, 1986).

Orange juice

A study which compared the effects of ingestion of 75 g of glucose and fructose with orange juice and water sweetened with saccharine as control in humans, reported that there was significant increase in generation of reactive oxygen species 2/h after consumption of glucose; no such effect was noted with either fructose or orange juice (which contain fructose and sucrose as predominant sugars) (Matthews *et al.*, 1987) or water (Ghanim *et al.*, 2007).

CONCLUSION

Fructose intake develops IR, hyperinsulinemia, hypertriglyceridemia and an increased likelihood for development of CVD. It has been suggested that fructose consumption leads to SNS stimulation and endothelial

dysfunction resulting in rise in BP. Adverse effects of fructose utilization are reportedly not manifest in female who are presumably protected because of the female sex hormones. However, fructose is not all that bad if consumed in limited quantities; fructose use does not upset glycaemic control rather an improvement in aforesaid may be achieved in patients with diabetes type-II resulting in lowered risk for CAD. Adequate seminal fructose concentrations help promote male fertility and that the natural sources of fructose, such as apples, honey and dates confer good to human health by increasing antioxidant levels and improved glycemic control.

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