Short Communication

Consumption of fructose-sweetened beverages for 10 weeks increases postprandial triacylglycerol and apolipoprotein-B concentrations in overweight and obese women

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Fructose consumption in the USA has increased over the past three decades. During this time, obesity, insulin resistance and the metabolic syndrome have also increased in prevalence. While diets high in fructose have been shown to promote insulin resistance and increase TAG concentrations in animals, there are insufficient data available regarding the long-term metabolic effects of fructose consumption in humans. The objective of the present study was to investigate the metabolic effects of 10-week consumption of fructose-sweetened beverages in human subjects under energy-balanced conditions in a controlled research setting. Following a 4-week weight-maintaining complex carbohydrate diet, seven overweight or obese (BMI 26·8–33·3 kg/m2) postmenopausal women were fed an isoenergetic intervention diet, which included a fructose-sweetened beverage with each meal, for 10 weeks. The intervention diet provided 15 % of energy from protein, 30 % from fat and 55 % from carbohydrate (30 % complex carbohydrate, 25 % fructose). Fasting and postprandial glucose, insulin, TAG and apoB concentrations were measured. Fructose consumption increased fasting glucose concentrations and decreased meal-associated glucose and insulin responses (P=0·0002, P=0·007 and P=0·013, respectively). Moreover, after 10 weeks of fructose consumption, 14 h postprandial TAG profiles were significantly increased, with the area under the curve at 10 weeks being 141 % higher than at baseline (P=0·04). Fructose also increased fasting apoB concentrations by 19 % (P=0·043 v. baseline). In summary, consumption of fructose-sweetened beverages increased postprandial TAG and fasting apoB concentrations, and the present results suggest that long-term consumption of diets high in fructose could lead to an increased risk of CVD.

Dietary fructose consumption in the USA has increased by about 30 % during the past three decades(1) and has coincided with a dramatic rise in the prevalence of obesity and its metabolic consequences2,3. There is substantial evidence from studies conducted in animals and some in human subjects to indicate that high-fructose diets can promote the development of the metabolic syndrome2,3,4. Fructose is primarily metabolised by the liver, where it is a highly lipogenic substrate5. In animals, fructose consumption enhances hepatic de novo lipogenesis6 and increases the secretion of apoB-containing VLDL particles7. Similarly, in humans, consumption of a high-fructose diet can increase both fasting8 and postprandial9 plasma TAG concentrations relative to diets containing starch or glucose. High-fructose diets can promote insulin resistance in animals by directly interfering with hepatic insulin signalling10–12; and the elevated postprandial TAG in response to fructose may further impair insulin sensitivity13. Consistent with these effects, overfeeding human subjects with a high-fructose diet for 6 d not only led to increased de novo lipogenesis and plasma TAG, but also reduced hepatic insulin sensitivity14.

Unlike glucose, fructose does not stimulate insulin secretion, due to its hepatic metabolism and the low level of expression of the fructose transporter GLUT5 in pancreatic β-cells15. The metabolic effects of long-term consumption of high-fructose diets have not been fully investigated in

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human subjects. In a short-term study in normal-weight women, we reported that consumption of fructose-sweetened beverages (providing 30 % of total energy) with meals resulted in lowered postprandial glucose and insulin excursions, reduced 24 h circulating leptin concentrations relative to when the subjects consumed glucose-sweetened beverages, and produced sustained increases of postprandial plasma TAG(16). The present study was designed to investigate the effects of an isoenergetic 10-week intervention, in which 25 % of daily energy requirements was provided as fructose-sweetened beverages, on fasting and postprandial glucose, insulin, TAG and plasma apoB concentrations.

Subjects and methods

Subjects

Seven overweight or obese (BMI 26.8–33.3 kg/m²) postmenopausal women (age 50–72 years) were recruited. All subjects provided informed consent to participate in the study, and reported being non-smokers, relatively sedentary and weight stable. Subjects were given a complete medical examination.

Experimental protocol

The experimental protocol was approved by the Human Subjects Review Committee at the University of California (Davis, CA, USA). Subjects resided in a residential facility during the entire 14-week period, where body weight, food intake and blood pressure were monitored. Body composition measurements and 14 h postprandial blood collections were performed at the Ragle Human Nutrition Research Facility (University of California, Davis, CA, USA). Exercise was performed at the Ragle Human Nutrition Research Facility (Davis, CA, USA). Subjects were given a complete medical examination.

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Subjects were studied at three different times: at the end of a 4-week baseline period (before dietary intervention) and at 2 and 10 weeks during the intervention. During the initial baseline period, subjects consumed a weight-maintaining diet. Energy requirements for weight maintenance were estimated using the Harris–Benedict equation(17) and with a physical activity period, subjects consumed a weight-maintaining diet. Energy intake was adjusted every fourth day to maintain body weight. Following this stabilisation period, subjects were fed 100 % of their established energy requirements. Body composition was assessed by the paired t test. The two-sided level of significance was set at P<0.05.

Results

Body weight, body composition and blood pressure

There was a small (about 1.5 %) decrease of body weight over the 10-week intervention period (Table 1). Body composition was not significantly changed, and blood pressure remained stable over the 10-week intervention.

Fasting plasma concentrations of glucose, insulin and lipids

Consumption of the fructose-sweetened beverages significantly increased fasting glucose concentrations at 2 weeks...
and 10 weeks \( P = 0.0002 \) v. baseline) (Table 1). Fasting plasma insulin concentrations and homeostatic model assessment of insulin resistance were not significantly increased. There were no significant effects of fructose consumption on fasting total cholesterol, LDL, HDL or plasma TAG concentrations (Table 1).

Postprandial glucose, insulin and triacylglycerol responses and fasting apolipoprotein-B concentrations

Consumption of fructose reduced meal-related plasma glucose excursions by 67% at 2 weeks and by 73% at 10 weeks (Fig. 1 (a)). The insulin area under the curve was reduced in subjects consuming fructose-sweetened beverages, by 42% at 2 weeks and 39% at 10 weeks, relative to baseline (Fig. 1 (b)).

Relative to the baseline diet, consumption of fructose-sweetened beverages resulted in a progressive increase of postprandial TAG concentrations. The TAG area under the curve was reduced by 44% after 2 weeks and by 141% at 10 weeks in subjects consuming fructose (Fig. 1 (c)). After 10 weeks of fructose consumption, fasting apoB concentrations increased by 44% after 2 weeks and by 141% at 10 weeks in subjects consuming fructose-sweetened beverages (25% of energy requirements) and increased postprandial TAG concentrations and fasting plasma apoB concentrations.

A major strength of the present study is the high degree of control over the subjects’ diets, with the subjects residing in a supervised setting and consuming standardised meals for the entire 14-week period. Another strength of the present study is that in addition to fasting concentrations, postprandial glucose, insulin and TAG responses were measured. Examination of only the fasting concentrations would not have revealed the marked effects of fructose consumption on postprandial TAG profiles. Subjects consuming the fructose-sweetened beverages for 10 weeks exhibited increased circulating TAG concentrations of \( > 1 \) mmol/l over fasting concentrations for the entire period from after lunch until 22.00 hours in the evening (Fig. 1 (c)). A number of studies support the existence of an independent relationship between non-fasting (postprandial) TAG concentrations and CVD(21,22). Moreover, because circulating apoB concentrations reflect the total number of potentially atherogenic lipoprotein particles, the increase of apoB concentrations observed here suggests that long-term consumption of high amounts of fructose could be atherogenic(23).

The main limitations of the present study are that the observations were restricted to overweight, postmenopausal women. Due to the high cost of the study, enrolment was limited to postmenopausal women, in order to avoid the possible confounding effects of age, sex and menstrual cycle on postprandial TAG metabolism(24,25).
The finding that consuming fructose-sweetened beverages promotes postprandial hypertriacylglycerolaemia is well supported by studies in animals fed high-fructose diets\(^{(1)}\), and by several studies in human subjects, although there are some conflicting results in the literature\(^{(2)}\). While the precise biochemical mechanisms underlying fructose-induced hepatic VLDL overproduction are unknown, studies in mice have shown that long-term fructose feeding induces the hepatic expression of a number of lipogenic genes, including stearoyl-CoA desaturase\(^{(26)}\). Other rodent studies indicate that protein tyrosine phosphatase-1B, a negative regulator of insulin signalling, is required for fructose-associated increases in VLDL secretion \(^{(27)}\). Impaired TAG uptake by adipose tissue, possibly due to reduced adipose tissue lipoprotein lipase activation from the lower insulin excursions, may also contribute to fructose-induced hypertriacylglycerolaemia in humans\(^{(28)}\). In the present study, the relative contributions of increased TAG production v. reduced clearance were not examined; however, this issue is currently being addressed in our ongoing studies. In human subjects, several short-term studies indicate that fructose consumption induces postprandial hypertriacylglycerolaemia\(^{(29–31)}\). In our previous study, consumption of fructose-sweetened beverages (30% of energy) with mixed-nutrient meals in normal-weight women led to a rapid and prolonged increase of plasma TAG concentrations compared with when the same subjects consumed an equal amount of glucose\(^{(16)}\). We have obtained similar results in overweight and obese men and women\(^{(32)}\). Bantle et al. fed men and women diets containing 17% of energy as either fructose or glucose for 6 weeks\(^{(9)}\). Men on the fructose diet had significantly higher fasting plasma TAG concentrations and 24 h circulating TAG responses than the men consuming glucose, but neither of these effects were observed in women. The lack of an observable effect...
of fructose on postprandial TAG concentrations in women may be due to differences in age between the women in present study (mean age 64 (SE 3) years) and those studied by Bantle et al. (9) (overall mean about 40 years). Postprandial TAG responses are known to be greater in older subjects (24). Other factors, such as the presence of obesity and/or insulin resistance, the amount of fructose included in the diet, and the use of in-patient v. out-patient studies may also explain the inconsistencies that have been observed between studies. The effects of fructose consumption on postprandial TAG may also be exacerbated by pre-existing hypertriglycerolaemia and hyperinsulinaemia (33,34). Study duration may also be an important factor for the development of postprandial hypertriglycerolaemia, as it was much more pronounced after 10 weeks of fructose consumption than at 2 weeks.

Drinking fructose-sweetened beverages as part of a weight-maintaining diet also increased fasting plasma glucose concentrations, while meal-related excursions of plasma glucose and insulin were reduced. These findings are consistent with our short-term results (16) and some (35), but not all, studies of human subjects (2). Increases of fasting plasma glucose concentrations, within the normoglycaemic range, have been reported to independently predict the development of type 2 diabetes in men (36).

The amount of added fructose (25 % of energy) investigated here is higher than the average US daily consumption, as the most recent estimate for the mean intake of added sugars by Americans (the 1994–6 Continuing Survey of Food Intakes by Individuals (37)) was 15.8 %. It is likely, however, that intake of sugar-sweetened beverages as well as total energy intake has increased in the 12 years since this survey, and is likely to be higher in certain groups, such as adolescents (38). Moreover, as sugar, fat and energy consumption are often under-reported in surveys (39), we propose that consuming 25 % of total energy as sugars is not uncommon. However, since high-fructose corn syrup and sucrose are the predominant sweeteners in the US food supply and are composed of approximately equal parts fructose and glucose, it is unlikely that fructose itself is often consumed at 25 % of total energy. Interestingly, we have preliminary data which demonstrate that high-fructose corn syrup and sucrose both increase postprandial TAG comparably to pure fructose alone, and to support the relationship between fructose consumption and elevated postprandial TAG and apoB concentrations in a larger group of overweight and obese male and female subjects (n 18) (40).

In summary, consumption of fructose-sweetened beverages as part of a weight-maintaining diet for 10 weeks increased fasting glucose concentrations, postprandial TAG concentrations, as well as fasting plasma apoB concentrations in overweight and obese postmenopausal women. Together, these results suggest that obtaining a significant proportion of daily energy intake from fructose may promote or exacerbate altered lipid and carbohydrate metabolism associated with the metabolic syndrome, the prevalence of which has increased dramatically in parallel with fructose consumption in the USA. Furthermore, the increased fasting apoB and postprandial TAG concentrations observed in response to fructose consumption suggest that prolonged consumption of diets high in fructose could contribute to an increased risk for development of CVD.

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There are no conflicts of interest to declare.

K. L. S., S. S. E., N. L. K. and P. J. H. designed the study; K. L. S., S. S. E., P. J. H. and J. L. G. conducted the study; M. P. C. and S. C. G. were physicians for the study; R. M. K. and N. L. K. provided intellectual input on study design and data interpretation; M. M. S. performed the statistical analysis and wrote the first draft of the manuscript, and all authors reviewed and provided input on subsequent drafts.

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