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FACTS BEHIND THE HEADLINES

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Is there really a link between diabetes and the ingestion of fructose?

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Fructose naturally occurs in fruits, so this carbohydrate is an inevitable constituent of a healthy, balanced diet. Compared with glucose, the monosaccharide fructose leads to a lower rise in blood sugar concentration after it is consumed and has minimal dependence on insulin for its metabolism. Hence, until recently, many researchers have perceived fructose to be a healthier alternative to other carbohydrates that contain glucose; these include the complex carbohydrate starch and the simple sugar sucrose, which contains an equal amount of glucose and fructose. By contrast, worry now exists among some researchers that fructose and fructose containing sugars, such as sucrose and high-fructose corn syrup (HFCS), are a major cause of fat accumulation in the liver (*i.e.* intrahepatocellular lipid). It is claimed that the accumulation of fat in the liver occurs more when ingesting sources of fructose than when ingesting sources of glucose, and so leads to greater hepatic insulin resistance and ultimately to type 2 diabetes (Stanhope & Havel 2008; Stanhope *et al.* 2009; Lim *et al.* 2010; Lustig 2010, 2013).

Although the belief in such a route to diabetes among some researchers is strong, how strong is the evidence? If the claim is right, how much fructose in our diets would lead to type 2 diabetes?

These questions have importance for pure fructose as well as for other fructose-containing sugars (*e.g.* sucrose). This is because pure fructose is found in many popular foods on the market such as 'sports drinks' and confectionery, and it is still under consideration as a substitute for both simple and complex carbohydrates intended for regular use by patients with diabetes (Sievenpiper *et al.* 2011, 2012b). It also raises concern about the fructose content of fruits, which is being promoted widely as part of the *5-A-DAY* message.

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Many research scientists and public health nutritionists recently attended the 2012 American Society for Nutrition meeting in the USA to hear the arguments (Bray 2013; Klurfeld 2013; Lustig 2013; Rippe & Angelopoulos 2013; White 2013), but rejected much of the research that suggested adverse effects of fructose and other sugars. The main reason behind this decision was that many of the studies were conducted in animals or in humans using doses of fructose far in excess of usual intakes among consumers.

Furthermore, an international workshop in Brazil concluded that the suggested negative effects of usual intakes of fructose (<100 g/day) are not evident when human data are systematically reviewed (Latulippe *et al.* 2013). Negative effects have been seen in highly reproducible studies of laboratory animals with excessive doses of fructose (>25–60% of energy intake) on elevated bodyweight, insulin resistance, fasting triglycerides, blood pressure, uric acid and low density lipoprotein cholesterol (Latulippe *et al.* 2013). However, these findings have not been reproduced in human studies at doses consistent with habitual diets.

Despite the strength of consensus reached by scientists in these meetings in North and South America, here in Britain, newspaper columns continue to report claims that fructose (and therefore sugars in our diet) is toxic and deadly, without any mention of the challenges to such opinions from the scientific community (Bosely 2013; Moore 2013; see also Macdonald 2013).

Conclusions similar to those reached in the scientific consensus meetings in Brazil and the USA arose also from individual meta-analyses of intervention studies comparing fructose with equal amounts of other carbohydrates and looking at bodyweight, blood glucose, glycated haemoglobin (a marker of blood glucose control) and blood lipids among both healthy individuals and patients with type 1 and type 2 diabetes (Livesey & Taylor 2008; Sievenpiper *et al.* 2009, 2012a, 2012c; Cozma *et al.* 2012; Ha *et al.* 2012; Wang *et al.* 2012). Likewise, a similar conclusion was reached when systematic reviews on other fructose containing sugars were considered, either with (Morenga *et al.* 2012) or

without (Ruxton *et al*. 1999, 2010; Dolan *et al*. 2010a, 2010b) the conduct of meta-analyses.

With all of the above in mind, two pertinent comments can be made. Firstly, dose appears to be important. A dose of fructose less than 100 g/day appears to be without the negative effects described in animals and may have some beneficial effects such as reduced blood glucose and glycated haemoglobin (blood markers for diabetes) (Livesey & Taylor 2008; Livesey 2009; Sievenpiper *et al*. 2012a). Likewise, whole-body insulin sensitivity is often claimed to be impaired by fructose consumption, generally based on very high doses in animal (up to 60% of food energy as fructose) or human studies (>150 g of fructose per day). However, whole-body insulin sensitivity in humans may be improved at usual fructose intakes of less than 150 g/day (Livesey 2009, 2011). Similarly, dose–response meta-analysis of the effect on glycated haemoglobin with up to 90 g/day of fructose found improvement in subjects with dysglycaemia (*i.e*. abnormally elevated blood glucose levels) (Livesey & Taylor 2008). Again, it is possible that fasting triglyceride concentrations fall to some extent when up to 100 g/day of fructose is consumed in place of other carbohydrates in healthy individuals (Livesey & Taylor 2008); other possible advantages of fructose in place of other carbohydrates have also been cited and include limited elevation of plasma urate, which has antioxidant properties, and potentially a longevity that is associated with a higher plasma urate concentration, as found in studies across animal species (Livesey 2009). Secondly, energy intake seems to be a major factor. The effect of excessive fructose ingestion on bodyweight appears to be caused by its energy content. Thus, intervention studies comparing either monosaccharide fructose or other fructose containing sugars isocalorically with other carbohydrates have revealed no significant difference in their effects on bodyweight (Livesey & Taylor 2008; Morenga *et al*. 2012; Sievenpiper *et al*. 2012c).

Epidemiological observations provide conflicting results of the potential of sugars to promote type 2 diabetes. A recent cross-country ecological study that included data from 136 to 141 countries (the number dependent on the model used to analyse the data) from all continents observed a positive association between sugar availability and the prevalence of type 2 diabetes (Basu *et al*. 2013). Although this study was well conducted for this type of investigation, it lacked causal inference, and the researchers were unable to obtain data for some important confounders. In particular, the study did not adjust for the level of educational attainment, country-specific dietary glycaemic load and alcohol intake, which interacts with glycaemic load and has a complex relation with the incidence and progression of type 2 diabetes. In addition, sugars available from all foods and drinks as captured by Food and Agriculture Organization (FAO) food supply data for individual countries (FAO 2011) as used in this study, take no account of food wastage or export to other countries. Together these factors have a greater influence across countries than within countries as a result of the wider range of intakes (Livesey 2010; Mekary *et al*. 2011; Livesey *et al*. 2013).

Likewise, another cross-country ecological study (43 countries across all continents) positively related HFCS availability to the prevalence of type 2 diabetes (Goran *et al*. 2013). However, this study also lacked causal inference and gave incomplete consideration to a range of factors that could affect the prevalence of type 2 diabetes. Furthermore, data in this study (Goran *et al*. 2013) have been analysed by the present author (G. Livesey, unpublished) who found no association in all of the 17 countries where HFCS availability was between 1 and 24 kg *per capita* (*i.e*. 3–65 g/day with no countries exceeding 65 g/day). Indeed, type 2 diabetes prevalence in this 'dose' range tended to be inversely associated with the availability of HFCS. Three within-country cross-sectional observational studies have also suggested a marked negative (inverse) association (Livesey 2009).

Although both the within- and the across-country cross-sectional observational studies provide a low level of evidence and are conflicting, the highest quality and most reliable observational studies are prospective cohort studies, and these have produced the most consistent findings to date. These studies indicate sucrose to have no impact or to be slightly negatively associated with the incidence of type 2 diabetes in both North America and Europe (Meyer *et al*. 2000; Janket *et al*. 2003; Montonen *et al*. 2007; Sluijs *et al*. 2013). Meta-analysis by the present author (unpublished) indicated for all studies combined that the relative risk (RR) of incident type 2 diabetes was not significantly different; cohorts of the lowest sucrose consumers in the sampled populations had RR = 1, compared to RR = 0.95 (95% confidence interval 0.80–1.09) for the cohorts of highest sucrose consumers.

What about recent suggestions that fructose has a unique ability to elevate the fat content of the liver as a first or early stage in the development of type 2 diabetes?

To date, randomised-controlled intervention trials (RCTs) in humans investigating whether fructose has

the ability to elevate the fat content of the liver are mostly limited to trials of excessive fructose intake over a short duration (Couchepin *et al*. 2008; Lê *et al*. 2009; Lim *et al*. 2010; Lustig 2010). These trials typically investigated the effects of excessive fructose intakes compared with a habitual diet that met energy requirements for bodyweight maintenance. The liver fat content of participants was ascertained while on the habitual diet (baseline) and again after the intervention in which the participants' energy intakes had been increased to well above their requirements by the administration of extra energy in the form of either fructose, glucose or saturated fat. The doses of fructose administered in these studies were so high (described below) that it was necessary to consume the major fraction of energy in drinks.

In one such study of healthy men, ~250 g/day fructose was ingested in a diet providing 135% of energy needs. Findings showed that the excess of energy from fructose raised liver fat content of participants by 16% in seven days. This response was no greater than was found for a similar excess of energy from saturated fat (Sobrecases, Le *et al*. 2010). These findings were confirmed by another study in which healthy men consumed ~200 g/day fructose while consuming 117% of their food energy requirements for 7 days. Together, these studies in healthy men indicate that the cause of fat accumulation in the liver was an excess of energy *per se* rather than an effect of fructose alone.

Additionally, two RCTs using the same design as those mentioned above, to compare the effects of fructose and saturated fat, have each shown that ~215 g/day glucose intake (in a diet providing 130–135% of energy requirements) was equally as effective as fructose in causing fat to accumulate in the liver (Ngo Sock *et al*. 2009; Lecoultre *et al*. 2013). A further publication reported on a medium-term study of 10-week duration of similar design, in which, ~168 g/day of sugars was ingested in a diet providing 125% of energy requirements and showed no difference between excessive intakes of fructose and glucose on fat accumulation in the liver of overweight/obese healthy men (Stanhope *et al*. 2009). Results from the women in this study were irrelevant even for excessive fructose intakes because of differences in liver fat content of the two treatment groups at baseline; the difference being 15 times greater than the reported treatment difference (Stanhope *et al*. 2009). A study of similar interventional design in healthy men and women (Silbernagel *et al*. 2011) provided subjects with 150 g of fructose for 4 weeks in a diet providing 123% of energy requirements. The ingested fructose was compared with the same amount of ingested glucose. Both of these sugars raised tissue fat to a similar extent as measured by visceral, subcutaneous, abdominal and skeletal muscle fat. Notably, too, both sugars raised liver fat content proportionately.

Furthermore, in these trials, the consumption of fructose was three to four times higher than the total amount of fructose ingested from all sugars, on average, in the USA (Marriott *et al*. 2009) and five to seven times higher than intakes in the UK (S. Gibson, personal communication); such excessive intakes raise concern about the relevancy of the findings to public health.

From the studies described on healthy people, it appears that fructose is not unique among sugars in its ability to increase fat storage in the liver. Moreover, it is possible that fructose intake needs to reach a threshold in excess of 17% of energy requirements before liver fat begins to accumulate (Lecoultre *et al*. 2013). This is an amount much greater than the 99th percentile for total fructose consumption per person from all ingested sugar sources in the UK (S. Gibson, personal communication) and equal to the 95th percentile of intake among the highest consumers of fructose in the USA. National (USA) data showed that during 1999–2004, these highest consumers were 19- to 22-year-old men ingesting 17.5% of food energy as fructose from all sources (Marriott *et al*. 2009). Fructose consumption peaked during this time and has fallen subsequently, probably because of a change in the US economy. Therefore, it is not evident at present that an elevated liver fat content is uniquely caused by dietary fructose, nor is it clear that choosing this particular type of sugar (or sugars containing fructose), in preference to other dietary carbohydrate, is the cause of type 2 diabetes in humans (subsequent to the accumulation of fat in the liver). Similarly, evidence at present is insufficient to suggest that fructose, more than fat or any other carbohydrates, is a major cause of non-alcoholic fatty liver disease (NAFLD) (Vos & Lavine 2013). Likewise, there is no convincing evidence that habitual fructose intakes could uniquely contribute to the liver's insulin resistance, either secondarily to, or independently of, liver fat accumulation. Consequently, there is doubt that fructose *per se* leads to the development of hyperinsulinaemia, metabolic syndrome and type 2 diabetes in accordance with the prior hypothesis (Stanhope & Havel 2008; Stanhope *et al*. 2009; Lim *et al*. 2010; Lustig 2010, 2013).

Although it is not evident that fructose has a unique ability to increase fat storage in the liver, it is possible that hepatic insulin resistance is not actually dependent on prior accumulation of fat in this tissue (Lecoultre

et al. 2013). Authors from two separate RCTs of one-week duration (Couchepin *et al*. 2008; Lê *et al*. 2009) have claimed that fructose (~245 g/day for one week) can increase hepatic insulin resistance. However, in both these RCTs, the lack of a comparative carbohydrate in the control groups made it impossible to infer whether extra fructose, carbohydrate or energy was causal. In another RCT of one-week duration in healthy young men, no significant difference in hepatic insulin resistance was found after consuming an excessively high-fructose diet compared with a similar diet contributing an equal amount of glucose in place of the fructose (Ngo Sock *et al*. 2009). By contrast, energy from either carbohydrate (fructose or glucose), when ingested in excess of food energy needs, resulted in liver insulin resistance significantly above the resistance at baseline by almost 20%. Most recently, authors of a RCT in healthy humans (Lecoultre *et al*. 2013) also concluded that excess energy intake from glucose increases hepatic insulin resistance to a similar extent as fructose. All these data are consistent with the 'amount of' sugars being more important than the 'type of' sugars in affecting hepatic insulin resistance. A similar conclusion has been reached in relation to patients with type 2 diabetes consuming fructose instead of sucrose (~13% of energy intake) for three months (Thorburn *et al*. 1990).

Are the potential negative effects of fructose partially limited by its incomplete absorption in adults, as suggested elsewhere?

It has been suggested (Lustig 2011) that the negative effects of fructose on human metabolism might be limited by its incomplete absorption in the body. Fructose malabsorption is evident in irritable bowel patients (de Roest *et al*. 2013) and fasted healthy people after ingesting 50 g of pure fructose in water. Evidence on fructose malabsorption in healthy adults in the fed state is less well known. Co-ingestion of glucose with fructose reduces fructose malabsorption in otherwise fasted individuals (Latulippe & Skoog 2011). Notably, too, in the context of other dietary substrates, none of the RCTs investigating the effects of high and excessive doses of fructose on metabolism (as discussed above) were aborted because of abdominal discomfort or diarrhoea; symptoms that would have been expected had appreciable monosaccharide malabsorption occurred. Likewise, interventions that provide 17%, 30% and 45% of food energy requirements as fructose in addition to a regular diet that met 100% of their energy requirements only resulted in mild symptoms of abdominal discomfort and bloating during the first day of fructose consumption; this was observed in only a few of the study participants and ceased spontaneously by the following day (Lecoultre *et al*. 2013). These observations would therefore suggest that a healthy human intestinal tract may have a very high capacity for fructose absorption in the context of a daily co-ingestion with a usual diet.

Fructose and sugars containing fructose are sources of food energy. In newly diagnosed patients with type 2 diabetes, sub-maintenance energy intake that leads to bodyweight reduction is important for optimal survival and metabolic control (Lean *et al*. 1990). Similarly, NAFLD is reversed by moderate energy intake and bodyweight reduction in the majority of cases (Eriksson *et al*. 2009; Musso *et al*. 2010; Sullivan 2010; Lim *et al*. 2011). As fructose and other sugars are sources of energy, excessive ingestion could promote weight gain, which is detrimental to the management of both type 2 diabetes and NAFLD.

What about sugars in drinks?

Energy from drinks has been suggested to be poorly recognised by the body's satiety signals, thus leading to markedly incomplete caloric compensation compared with the same proportion of sugars in solid foods. A potential consequence of this is that sugary drinks pose a greater risk for higher bodyweight than sugars in solid foods (Rolls *et al*. 1990; Mourao *et al*. 2007; Mattes & Campbell 2009). However, not only have these studies been conflicting but they also have been noted for several methodological problems (Almiron-Roig *et al*. 2004). These problems included poor design, use of appetite rating rather than measurement of food intakes and short duration of intervention, which makes it difficult to predict the long-term effect of consuming sugar-sweetened drinks on energy balance, weight maintenance and type 2 diabetes.

If total energy intake is increased by the consumption of sugar-containing drinks, then it has been proposed that almost full caloric compensation to such 'liquid calories' arises spontaneously within one to two years (Livesey 2010). The proposal arose because the rate of bodyweight gain caused by consuming such drinks in longitudinal studies (prospective cohort and interventional) fell progressively over time to 98% less than expected had all the energy from the drinks been stored in adipose tissue, accounting for changes in energy expenditure as a result of changes in bodyweight. Consequently, gain of a higher steady-state bodyweight in the longer term when consuming higher than usual amounts of sugars in drinks tends to be limited to

1–2 kg (Malik *et al*. 2006; Forshee *et al*. 2008; Morenga *et al*. 2012). Extrapolations from medium-term studies approaching such weight gains caused by consuming sugar-sweetened drinks, *e.g*. up to six months (Maersk *et al*. 2012), could not then be expected to reflect the long-term outlook for obesity, which pertains to a much higher weight gain. Therefore, weight gains higher than 1–2 kg (as seen in obesity) must have other causes. Consistent with this, a prospective cohort study was unable to show that adult bodyweight was related to the amount of sugar-sweetened drinks habitually consumed, although temporal changes in bodyweight occurred in association with a voluntary change in daily intake of sugar-sweetened drinks (Schulze *et al*. 2004).

Sugar-sweetened drinks are thought to include soft drinks, fruit drinks, iced teas, energy drinks and vitamin water drinks. Frequent consumption of these drinks is thought to moderately elevate the risk of type 2 diabetes. Consistent observational evidence in favour of this risk has been obtained in a convincing number of prospective cohort studies (Schulze *et al*. 2004; Montonen *et al*. 2007; Palmer *et al*. 2008; Malik *et al*. 2010; de Koning *et al*. 2011; Fagherazzi *et al*. 2013; Sakurai *et al*. 2013; TIC 2013). However, the direct role of fructose *per se* in drinks has been questioned by many of the studies' authors. Possible explanations for the association between sugar-sweetened drinks and the incidence of type 2 diabetes, in part or in total, include a pre-existing association between body mass index (as a measure of adiposity) and sugar-sweetened drink consumption (Fagherazzi *et al*. 2013; TIC 2013); an elevation of glycaemic load from drinks sweetened with sucrose or HFCS (Livesey 2010; Malik *et al*. 2010; Livesey *et al*. 2013); and based on observations on people who drink sugar-sweetened drinks, a consumption of less dietary fibre and magnesium (Schulze *et al*. 2004). Similar explanations arise when trying to explain the elevated risk of either type 2 diabetes or metabolic syndrome associated with artificially sweetened beverages (*i.e*. drinks containing no fructose) in observational studies (Dhingra *et al*. 2007; Nettleton *et al*. 2009; Fagherazzi *et al*. 2013; TIC 2013).

Conclusion

Considering all the evidence, the association between fructose in drinks and type 2 diabetes has been deemed limited and too unreliable to merit governmental action via various agencies in the USA (Klurfeld 2013). Subsequently, there is a need for further research to focus on sugars in drinks in general rather than on sources of fructose such as HFCS (Klurfeld *et al*. 2013). Until more is known, labelling of such drinks to alert consumers to their energy content and provision of 'diet-' or 'zero-energy' drink options for consumers would appear to be a responsible precautionary measure, providing of course that package labelling is in compliance with relevant food information regulations, such as those in the European Union (EU 2011).

Conflict of interest

Geoffrey Livesey holds shares in Independent Nutrition Logic Ltd, an independent consultancy that takes commissions from many organisations, a full list of which may be found at www.inlogic.co.uk. However, the views expressed in this article are those of the author alone.

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