Conference on 'Carbohydrates in health: friends or foes'
Symposium 2: New perspectives on carbohydrates and health

Relevance of liver fat to the impact of dietary extrinsic sugars on lipid metabolism

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In contrast to the decline in mortality from many non-infectious, chronic diseases in the UK, death from liver disease has increased exponentially in men and women over the past 40 years. This is primarily because of the over consumption of alcohol, but also the increased prevalence of obesity, which is linked to early pathology through the accumulation of liver fat. Supra-physiological intakes of fructose-containing sugar can produce acute, adverse effects on lipid metabolism, and deliver excess energy that increases bodyweight and the deposition of fat in sites other than adipose tissue, including the liver. This review addresses the variable metabolic origins of liver fat, and the key importance of postprandial lipid metabolism in this respect. The effects of supra-physiological intakes of sugar are also considered in context of the real world and established threshold for the adverse effects of sugar on cardio-metabolic risk factors. The review concludes that while the average intake of sugar in the UK falls well below this critical threshold, intakes in subgroups of adults, and especially adolescents, may be cause for concern. There is also evidence to suggest that raised liver fat, acquired, in part, through an impaired removal of postprandial lipaemia, can increase sensitivity to the adverse effects of sugar at all ages.

Liver fat: Sugar: Fructose: Sucrose: Plasma TAG

The outcome of short-term interventions with excessive amounts of sugar have fuelled debate over the impact of sugar on obesity and cardio-metabolic disease, and contentious claims that fructose is toxic to health and even the new tobacco. Although the latter have been highly emotive in generating adverse publicity for sugar through the media, they have misled the public's understanding of how sugar intake translates to disease risk in the real world. Raised liver fat is increasingly recognised as a progenitor of advanced liver disease, and origin of cardio-metabolic risk, especially risk mediated through plasma lipids. To understand how sugar impacts on cardio-metabolic risk in populations, it is vital to interpret the outcome of acute interventions with excessively high amount of sugar, in perspective of much lower, every day intakes. It is also worth considering that raised liver fat may act as a pre-existing metabolic disposition that could potentially increase sensitivity to the adverse effects of sugar.

Non-alcoholic fatty liver disease, dyslipidaemia and cardio-metabolic risk

The accumulation of ectopic fat in the liver (hepatosteatosis) is known to precede the development of the inflammatory condition steatohepatitis, which can progress to severe and often terminal liver disease[1]. While the overwhelmingly high prevalence of fatty liver in westernised, pre-clinical populations is likely to have a multi-factorial aetiology, two of the most prominent causes are alcohol and obesity. The exclusion of alcohol abuse as a cause, defines non-alcoholic fatty liver disease (NAFLD), which although considered by many to be clinically


Abbreviations: DNL, *de novo* lipogenesis; LPL, lipoprotein lipase; NAFLD, non-alcoholic fatty liver disease.
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benign in its self, has been implicated as a major underlying cause and/or effect of increased CVD[2]. The definition of NAFLD (liver fat >5 %) does not totally exclude alcohol, but has upper limits of intake of 20 and 30 g/d for women and men, respectively. This renders the term NAFLD something of a misnomer, given that in reality it is impossible to discriminate between the individual contributions of obesity and a moderate, habitual intake of alcohol to this condition. Moreover, because the identification of NAFLD relies on quantitative imaging techniques, such as MRI, or invasive liver biopsy, it is likely to be an under-diagnosed condition, with a higher prevalence in the free-living populations than that reported in the literature (30 % non-obese and 75 % obese)[3].

Cardio-metabolic risk describes a clustering of risk factors that increase risk of CVD, including hyperglycaemia, dyslipidaemia, hypertension and vascular dysfunction. These factors are closely associated with insulin resistance and the accumulation of visceral and ectopic fat in the liver[4–6]. Visceral fat, as opposed to more superficially located subcutaneous fat, is located centrally in the abdomen around internal organs, and characterised by larger, hypertrophic adipocytes which express a relative lack of insulin sensitivity and an inflammatory phenotype. Ectopic fat is found inside liver, skeletal muscle, heart and pancreas and can be associated with metabolic dysfunction of the tissue. Excess visceral fat has been strongly associated with insulin resistance and increased CVD risk[5], and characterises a form of obesity which falls outside the conventional definition of obesity (BMI > 30)[7], and could be referred to as 'metabolic obesity'. Individuals with this form of obesity as identified by MRI have been described as being thin on the outside and fat on the inside[8]. An excess of visceral fat and NAFLD, in either classic or metabolic obesity, is strongly associated with a dyslipidaemia that features pro-atherogenic changes in plasma lipoproteins in the post-absorptive state, consisting of moderately raised plasma TAG, low HDL, and predominance of small, dense LDL, together with enhanced postprandial lipaemia. The latter provides an elevated concentration of plasma TAG that can remodel lipoproteins (LDL and HDL) into the smaller and denser particles that characterise the dyslipidaemia[9].

What are the metabolic origins of liver fat?

Excess TAG in the liver, also known as intracellular hepatic lipid, has several possible origins (Fig. 1). Firstly, the liver can synthesise its own fatty acids and TAG by *de novo* lipogenesis (DNL). In comparison with other mammals, the synthesis of fatty acids in human subjects is an underutilised pathway, since the bulk of lipid transported into the liver is as pre-formed fatty acids, mono-, di- and TAG. Stable isotope trace-labelling studies have shown that DNL makes a relatively small contribution to liver fat in the fasted state (<5 %) which increases with feeding (>20 %)[10]. Postprandial DNL is also significantly
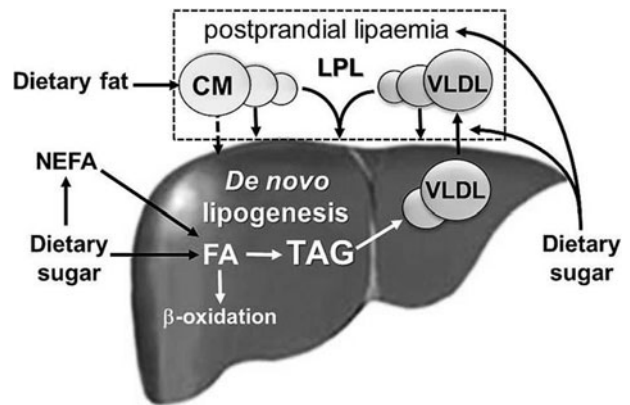
Fig. 1. Metabolic sources of liver fat: *De novo* lipogenesis (synthesis of fatty acids (FA) and TAG from dietary sugar); exogenous lipids, including NEFA, and lipoproteins from the lipoprotein lipase (LPL)-mediated lipolysis of intestinally derived chylomicrons (CM) and liver derived-VLDL. Production of CM is determined by amount and quality of dietary fat. Production and postprandial lipolysis of VLDL is influenced by dietary sugar.

up-regulated in both young and elderly patients with NAFLD[11,12], and by a high carbohydrate diet and more specifically, fructose through the transcriptional activation of lipogenesis[13,14]. However, DNL is difficult to measure and to interpret, and its original contribution to the effects of dietary sugar on liver fat is now believed to be overestimated[15]. A second source of lipid supply to the liver is NEFA from adipose tissue, which are typically released by the intracellular lipolysis of stored TAG in the post-absorptive phase and supressed by feeding (postprandial phase) under the regulation of insulin[16]. Plasma NEFA have been implicated in the oversupply of lipid to the liver in obese states, as a result of insulin resistance in adipose tissue, though it is possible that a compensatory increase in insulin secretion can suppress NEFA release in classically obese subjects[17]. Nevertheless, trace-labelling studies have revealed that plasma NEFA may account for the majority of liver TAG in obese NAFLD patients (59 % NEFA, 26 % DNL and 15 % diet)[11]. Excess visceral fat may be of particular relevance in this situation, given its greater tendency to release NEFA in the postprandial phase, as a result of its relative insulin resistance and responsiveness to hormones that oppose the actions of insulin[16,17]. The location of visceral fat, which is proximal to the liver, may also provide this storage depot with a short-cut for the delivery of its NEFA to the liver via the portal circulation. Finally, TAG-rich lipoproteins of intestinal and hepatic origin, that are in various stages of delipidation in the postprandial circulation[18], represent a substantial pool of lipid that could contribute to the accumulation of liver fat. The duration of postprandial lipaemia produced in response to the absorption of dietary fat from a single meal lasts in the order of 5–6 h. Since this period naturally overlaps with the frequency of fat consumed in meals, most free-living human subjects will be in a postprandial state throughout the day, and depending on meal timing, throughout the evening, and while asleep. The magnitude

of postprandial plasma is essentially determined by the rate of production and clearance of TAG-rich lipoproteins[9]. While most circulating TAG is derived from the diet and transported in chylomicrons, a variable fraction of the TAG will be carried by VLDL particles, which outnumber chylomicrons. These plasma lipoproteins of intestinal and hepatic origin compete for the action of the rate-limiting endothelial lipase, lipoprotein lipase (LPL), which lipolyses their TAG. The extent of this competition for LPL will determine the extent and duration of lipaemia, and can be influenced by the concentration and composition of the competing lipoproteins. The activity of LPL in adipose tissue and release of VLDL from the liver is also up and down-regulated by insulin, respectively, for the purpose of removing dietary fat from the circulation. These mechanisms help to explain why insulin resistance can promote enhanced postprandial lipaemia, through failure to suppress the export of VLDL from the liver and via increased competition for LPL.

The reason for elaborating on the details of these different sources of liver fat is to highlight that dietary fructose and sucrose have the potential to influence each of these pathways (Fig. 1). Dietary glucose and fructose are absorbed in a similar fashion from the gut, but while glucose is released to peripheral tissues, fructose is retained and metabolised by the liver. It by-passes a critical inhibition feedback step in glycolysis, and as such provides a source of energy and fat that is unregulated by the control of insulin and energy status of cells. In the short term ($\leqslant 6$ h), stable isotope trace-labelling studies reveal that over half the amount of ingested fructose can be converted to glucose, while approximately a quarter is converted to lactate leaving only a small percentage to be directly converted to plasma TAG (<1 %)[15].

Influence of dietary sugar (sucrose and fructose) on lipid metabolism and body weight

Dietary sugar has once again re-emerged at the top of the nutritional agenda as a potential underlying cause of obesity, diabetes and CVD[19], not least because of a frenetic crusade by meta-analysers and the media to diminish the link between saturated fat and CVD. The understanding of how sugar influences these conditions is complicated by the inextricable links between energy intake, weight gain and the specific cardio-metabolic effects of fructose and sucrose, which may be mediated, in part, through the development of NAFLD. Recent guidelines from the WHO and Scientific Advisory Committee on Nutrition in the UK to reduce sugar intake to a mean of less than half of our present intake (5 % of total energy) have heightened public awareness of the impact of sugar on health[20,21]. They have also rekindled concern for the chronic, overconsumption of sugar in the adolescent population in the UK, in relation to the staggeringly high prevalence of NAFLD in the obese and non-obese populations.

Carbohydrate-induced hyper-triacylglycerolaemia, although previously recognised as a possible link between sugar and cardiovascular health, has now assumed much greater significance as a phenomenon associated with the role of free sugars in NAFLD-related cardio-metabolic risk. Originally perceived as an acute, metabolic adaptive response to a high carbohydrate diet produced by a transient shift in substrate oxidation in the liver, its adverse effect in lowering HDL-cholesterol was largely responsible for the recommendation that low fat, high carbohydrate diets should not be recommended for reducing CVD risk[22]. It is now clear that moderately raised plasma TAG is a risk factor for CVD that is associated with all the classic features of metabolic syndrome, including NAFLD[6]. There is also good evidence that carbohydrate-induced hyper-triacyl-glycerolaemia is not simply an acute or transient phenomenon, but underlies the association between a high intake of carbohydrate and raised plasma TAG in populations[21].

The metabolic effects of dietary fructose and sucrose on lipid metabolism, body weight and NAFLD have been extensively reviewed recently[23–26]. This has coincided with a furore over the link between sugar and health, and the adverse outcomes of short-term, mechanistic studies that intervened with excessive amounts of fructose or sucrose (>20 % total energy) from sugar-sweetened beverages[27–31]. Reassuringly, the outcome of these studies have not been reproduced in interventions with moderate intakes of fructose or sucrose, especially under iso-energetic conditions, and are thus unlikely to translate to the effects produced by habitual intakes of sugar. Both glucose and fructose supplements have been shown to raise plasma TAG and liver fat in overweight men under hyper-energetic conditions, suggesting that these effects may not be specific to fructose, but mediated through an excess intake of energy[32,33]. Controversially, a recent meta-analyses concluded that there was a 'low level of evidence' that fructose and glucose actually exert similar effects on liver fat, and that present evidence to link fructose and sucrose with the development of NAFLD was insufficiently robust to draw conclusions[26].

Threshold effects of dietary fructose relative to present intakes in adults and adolescents

A dose–response relationship between the intake of fructose and plasma TAG has been show to exist in a meta-analysis, with a critical intake threshold of $\leqslant 100$ g/d, below which fructose exerts no effects on plasma TAG or body weight, and may even improve glycaemic control[34]. These findings are supported by data on the relationship between plasma TAG and increasing fructose intake in the National Health and Nutrition Examination Survey, which revealed no effects of increasing fructose intakes up to 100 g/d on plasma TAG, but a gradual and consistent fall in HDL-cholesterol up to this threshold (Fig. 2)[35]. The existence of an upper-intake threshold for the effects of dietary fructose
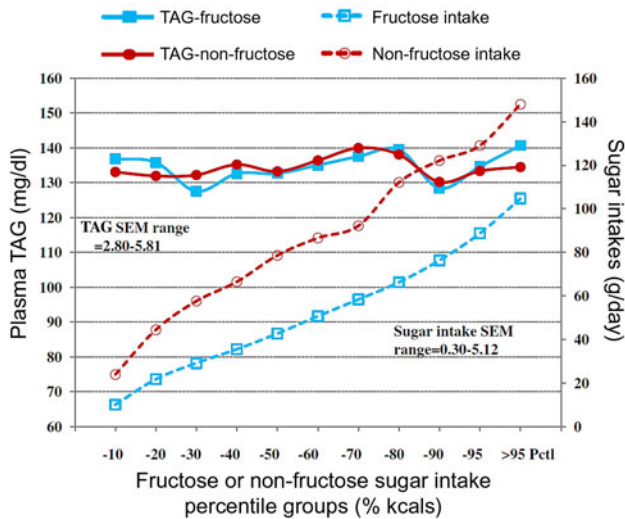
Fig. 2. Graph shows relationship between the concentration of plasma TAG (mg/dl) and intake of fructose and non-fructose sugar (expressed in percentile group of energy intake (% kcals) and g/d) in adults in the National Health and Nutrition Examination Survey[35].

on plasma TAG is further supported by studies in both normal and overweight men consuming everyday amounts of sucrose and fructose (about 10 % total energy)[36–38]. A rough conversion of 100 g/d fructose into energy intakes for adult men and women gives approximately 15 and 19 % of total energy, respectively. By comparison with intakes of sugar (non-milk extrinsic sugars) in the UK population, it is clear that average intakes in both adult men and women fall well below this threshold of fructose intake (about 6 %), given that a minimum of 50 % of this sugar will be fructose within sucrose (Fig. 3). Of much greater concern is the intake in the upper 2·5th percentile, especially for adolescent boys and girls, some of whom will almost certainly exceed this threshold[39].

Despite continuing debate over the impact of hyper and iso-energetic intakes of fructose-containing sugars, it is clear that additional energy from fructose, either as a mono or disaccharide in sucrose, will influence body weight. This provides fructose-containing sugar with the potential to exert adverse effects on blood lipids and liver fat through the direct metabolic effects of fructose and/or via weight gain[40,41]. While there is evidence to suggest that sugar can increase plasma TAG without affecting body weight[42,43], variation in energy intake, propensity to gain body weight (overriding energy compensation mechanisms), and the overall sensitivity of an individual to the metabolic effects of sugar, are all factors that have confounded the identification of effects of sugar that are independent of body weight. The expression of NAFLD provides a plausible explanation for the variation in the metabolic response to sugars, since this provides a direct link between fructose-containing sugar and plasma TAG via the synthesis and secretion of VLDL. It is also associated with changes in TAG-rich lipoproteins that are known to augment postprandial lipaemia.

Does enhanced postprandial lipaemia underlie the inter-relationships between dietary sugars, blood lipids and liver fat?

In 1979 a lipid biochemist, Donald Zilversmit, had the foresight to conclude that atherogenesis was a postprandial phenomenon[44]. A present review of the literature reveals an overwhelming body of evidence to support his conclusion, and explains why enhanced postprandial lipaemia should be of such key importance to cardiometabolic disease. It also provides a possible route by which sugar could promote NAFLD and dyslipidaemia, and thus a mechanism for the frequently observed variation in the sensitivity to the effects of dietary sugar on blood lipids.

As described earlier, enhanced postprandial lipaemia and NAFLD are common features of both classic (BMI > 30) and metabolic (BMI < 30) forms of obesity. The presence of NAFLD has been shown to enhance the postprandial response to fructose in obese children[45] and adults[46], and is characterised by an abundance of large chylomicrons and large, TAG-rich VLDL[47]. The latter are produced when liver fat is increased[48], and have been implicated as determinants of enhanced postprandial lipaemia by competing more avidly with chylomicrons for LPL[49]. This mechanism may explain why moderately raised plasma TAG (>1·5 mmol/l) in the fasted state predicts enhanced postprandial lipaemia. It may also contribute to the variable response of plasma TAG to dietary sugar that has been reported in seemingly healthy individuals with normal blood lipids measured in the fasted state[23].

From a dietary perspective, fructose, sucrose and SFA tend to increase liver fat and enhance postprandial lipaemia, and thus produce the opposite effects to that of PUFA[50,51]. With respect to the latter, long-chain n-3 PUFA from fish oil (e.g. DHA) are particularly effective in reducing postprandial lipaemia and liver fat[52]. Similarly, loss of body weight and physical exercise produce a marked attenuation of postprandial lipaemia[53], and also reduce liver fat[54]. A recent systematic review of postprandial studies revealed positive effects of fructose and sucrose on postprandial lipaemia, but only under hyper-energetic conditions in young healthy men[55]. It could not exclude the possibility that an iso-energetic exchange of fructose for other sugars or fats would produce significant effects on postprandial lipaemia in overweight and obese men. Moreover, the apparent threshold for the effect of fructose on plasma TAG of 100 g/d was reported to be reduced to 50 g/d for post-prandial measures[34]. Taken together, these findings provide compelling evidence to suggest that the sensitivity to fructose and sucrose may be mediated, in part, through an inter-relationship between the expression of NAFLD and postprandial lipaemia as seen in young children (Fig. 3)[56].

In conclusion, the consensus from systematic reviews on this popular topic is that there is presently insufficient evidence to link the metabolic effects of fructose *per se* with increase in body weight, and that excess energy intake in the majority of studies makes it impossible to
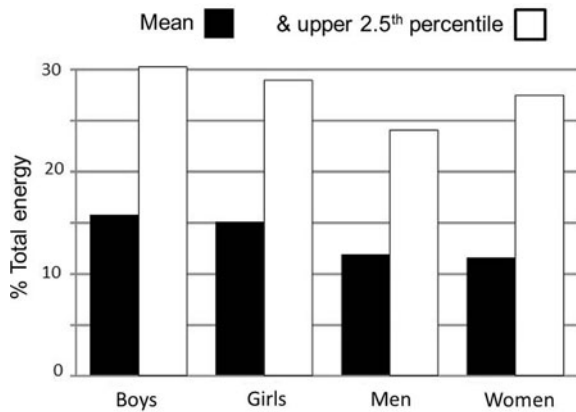
Fig. 3. Dietary intake of non-milk extrinsic sugars in adult men and women, and adolescent boys and girls in the UK. Data are taken from the National Diet and Nutrition Survey[39]. Closed bars denote mean intake and open bars intake in upper 2·5th percentile. Data are expressed as percentage of total energy.

disentangle the effects of body weight from the specific metabolic effects of sugar[25,26]. Likewise, the impact of habitual intakes of sugar on NAFLD also remains unresolved. Within populations, sugar is probably no more 'toxic' in terms of its potential to cause disease than dietary fat, both of which provide energy, which if passively over consumed, will exceed compensatory mechanisms and promote weight gain and obesity. The difference between these two macronutrients is that sugar is non-essential to our diet and reducing sugar intake is unlikely to produce any detrimental effect on health. Conversely, such a recommendation is likely to reduce risk of cardiometabolic and liver disease in subgroups of the population with a pre-existing metabolic disposition to the adverse effects of sugar, which might include raised liver fat. With this and recent guidelines in mind, it would seem more sensible to focus on limiting energy intake from sugar to prevent obesity, than trying to avoid upper thresholds of intake and the adverse metabolic effects of sugar.

Authorship

The author had sole responsibility for all aspects of the preparation of this paper.

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