International Journal of Obesity (2016) **40,** S1–S5

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REVIEW

Sweeteners and health: findings from recent research and their impact on obesity and related metabolic conditions

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Few topics in nutrition engender more controversy than added sugars in general, and fructose-containing sugars in particular. Some investigators have argued that added sugars are associated with increased risk of obesity, cardiovascular disease, diabetes, non-alcoholic fatty liver disease and even sugar 'addiction'. Other investigators have questioned the scientific basis for all of these assertions. This debate has extended far beyond the scientific community into various media outlets including the internet and other non-refereed venues often with heated rhetoric and little science. Against this backdrop, a group of experts and researchers in the metabolism and health effects of added sugars presented a symposium 'Sweeteners and Health: Findings from Recent Research and their Impact on Obesity and Related Metabolic Conditions' at the European Congress on Obesity on 7 May 2015. The papers in this supplement are based on the presentations made at this meeting. The current article is intended to serve as an Introduction to this supplement.

International Journal of Obesity (2016) **40,** S1–S5; doi:10.1038/ijo.2016.7

INTRODUCTION

Few topics in all of nutrition presently engender as much controversy as added sugars.[1–16] It has been argued that added sugars (particularly those containing fructose) may be associated with increased risk of obesity,[6,17] cardiovascular disease[18,19] and diabetes.[6,20] The rhetoric in this debate has become truly extraordinary with several investigators claiming that added sugars are 'toxic' and another summoning the book written by John Yudkin in the 1950s calling sugar 'pure, white and deadly'.[21] Inflammatory headlines in the popular press have even declared 'Death by Sugar' or 'Sugar, Drastic Measures'. Even prestigious medical journals, such as the *British Medical Journal*, have posted in its group blog an article entitled 'Sugar is the new Tobacco'.[22] The prestigious *New York Times* devoted a cover story in their magazine entitled 'Sweet and Vicious' with a picture of a disintegrating sugar cube on the cover while asking the question 'Is Sugar Toxic?'.[23] A well-known nutrition writer in the *New York Times* uncritically accepted the notion that sugar causes diabetes while writing a column entitled 'It's the Sugar, Folks'.[24]

That sugar[25] or carbohydrate at large[26] was responsible for the development of obesity has already been proposed in the past, but the pathophysiological mechanisms accounting for carbohydrates being more obesogenic than lipids or protein remained largely hypothetical. The proposal that insulin was key in favoring body fat gain[27,28] was at the origin of very-low carbohydrate diets, protein-sparing modified fast and the Atkins diet, which were popular (and still are) in the 1970s. These diets actually achieved significant, sometime substantial short-term weight losses,[29] but were associated with high rates of obesity relapse in the long term.[30] In addition, carefully performed, controlled trials indicated that similar weight reductions were observed with carbohydrate-free and -containing, energy-restricted diets, casting doubt about the causal role of carbohydrate or insulin in the pathogenesis of obesity.[31]

Putative pathogenic mechanisms and dietary interventions thereafter focused mainly on saturated fat, until there was a recurrence of interest, this time specifically on sugars at the turn of the millennium. Ironically, it started with the hypothesis that consumption of high fructose corn syrup (HFCS), which increased markedly in the 1970s and 1980s, was primarily responsible for an increase in obesity because of its alleged high fructose content.[17] This idea was based on the misconception that HFCS contains substantially more fructose than sucrose. This assumption was wrong. It is now recognized that one of the commonly used forms of HFCS (HFCS-55) contains only marginally higher amounts of fructose than sucrose. It should be noted that the other commonly used form of HFCS (HFCS-42) contains less fructose than does sucrose (42% vs 50%).[10] Furthermore, several well-controlled studies have documented that HFCS and sucrose have no significantly different effects on metabolism.[32–35]

With this return in interest about fructose, numerous studies have evaluated its short- and medium-term effects in humans and animals. They reported that diets very high in fructose, particularly in the setting of excess energy consumption, were indeed associated with increased plasma triglyceride and uric acid concentrations, and with increased hepatic glucose production. These findings have led to the publication of many non-critical reviews or summaries pointing to potential deleterious effects of fructose-containing caloric sweeteners, and to several organizations such as World Health Organization,[36] Scientific Advisory Committee on Nutrition in England[37] and American Heart Association[38] proposing to markedly reduce added sugar consumption. These reviews have been criticized by some scientists who argue that some of their main conclusions were not supported by systematic reviews and meta-analyses, randomized clinical trials[34,39–41] or of prospective cohort studies,[42–47] which should be at the top of the pyramid of evidence.[48]

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Interestingly, fructose had previously been the focus of much interest in the 1980s. At this prior time, it had been recognized that fructose metabolism did not require insulin, and that fructose ingestion elicited only modest increases in blood glucose. This led to the proposition that fructose may be an ideal sweetener for subjects with type 2 diabetes. To further support this proposal, several clinical studies assessed the effects of pure fructose replacing sucrose or starch on blood glucose concentrations of healthy subjects and of diabetic patients. These studies unequivocally documented that fructose efficiently decreased glycemia and hemoglobin A1c concentrations in subjects with diabetes.[43] The use of fructose as a prime sweetener for diabetic subjects was, however, not retained because of the occasional occurrence of hypertriglyceridemia.[49]

The past and present literature on the health effects of fructose is intricate, which explains why interpretation of results is so difficult and why dietary recommendations regarding fructose-containing sugars are so controversial. This literature includes many small-scale studies, inadequate to address the long-term health effects in humans, but each designed to address one specific aim at a time. One may schematically classify such studies into several large groups:

- Animal (mainly rodents) models.

These are studies in which obesity and diabetes mellitus were induced by a high fructose or sucrose diet.[50] The aim of these experiments was primarily to induce metabolic diseases in animals to identify pathophysiological pathways, or to run preclinical studies on candidate drugs. Such studies clearly demonstrated that fructose can induce metabolic diseases when given in excess. These studies do not compare the fructose to isocaloric amounts of other nutrients, however, and hence cannot demonstrate that fructose is more obesogenic than other dietary constituents. It should also be noted that high fat diets can be used as an alternate mean to induce metabolic diseases in animals.[51,52]

- Studies having compared pure fructose with glucose, sucrose or starch.

Most of these studies were primarily performed to search for beneficial effects of fructose on glycemia, but were not designed for long-term effects on blood triglycerides or on other health markers. Some studies used isocaloric replacement of other nutrients with fructose, whereas others merely added fructose to the existing diet,[42–48] which further adds to the confusion.

- Short-term controlled studies having assessed the effects of supplementation or nutrient replacement with fructose, glucose or other sugars on surrogate markers of metabolic health.

These studies allow evaluating the effects of a diet containing very high amounts of iso- or hypercaloric fructose-containing caloric sweeteners in humans. Such studies usually compare high sugar vs low sugar diet, but rarely include a comparative arm with fat or starch overfeeding.[53–55] They are to some extent the human counterpart of animal models, and provide useful information on metabolic pathways used for sugar metabolism, and on potential pathogenic mechanisms related to metabolic diseases. As pointed out by White,[11] however, many of these studies use doses of fructose far in excess of normal consumption often exceeding the 95th percentile population consumption level for the high sugar arm.

- Randomized controlled clinical trials assessing the effects of increasing or decreasing fructose-containing caloric sweeteners consumption.

These studies address the really relevant issue, that is, would interventions specifically targeted to sugar consumption be efficient to correct metabolic diseases. These studies altogether indicate that increasing sugar intake leads to body weight gain in adults, and that sugar reduction leads to body weight loss in children.[56] Adherence to intervention is a key factor in such studies, which globally evaluate the acceptability and efficiency of a dietary prescription on body weight or markers of metabolic health. The fact that non-sugar nutrient intake is not monitored, however, precludes accurate interpretation of underlying mechanisms.

- Epidemiological prospective cohort studies, evaluating the mathematical association between changes in fructose-containing caloric sweeteners consumption over time on the one hand, and changes in body weight or occurrence of specific diseases on the other hand.

These studies can assess whether or not a causal role sugars is plausible, but of course cannot prove causality.[56] Many of these studies did not assess simultaneously the role of other nutrients. When this was done, consumption of sugar-containing foods (mainly sugar-sweetened beverages) and also of sugar-free foods were associated with body weight gain.[57]

- Various mechanistic, observational or intervention studies *in vitro*, *ex vivo* or in animal/humans assessing the effects of fructose-containing caloric sweeteners on a wide array of end points, such as blood concentration of gut hormones, activation of brain areas involved in food intake controls, and so on.

Several recent studies in this category have attracted considerable attention by showing that fructose and glucose have different effects on the activity of brain areas involved in food intake control.[58,59] These cutting-edge reports will certainly yield important information in the future. Recent progresses in neurosciences and psychology also started unraveling the complex mechanisms controlling food intake behavior, and the existence of multiple-level regulations, including homeostatic and hedonic control systems, and will likely provide important information regarding caloric and non-caloric sweeteners in the future.[60] It should be pointed out that many of these studies published to date compare pure fructose to pure glucose, neither of which is typically consumed in isolation or use large dosages, or atypical means of delivery (e.g., intravenous).

The literature regarding sugars' metabolic effects is very large, and addresses a whole range of sugars' biological effects. For us scientists, this is a true Ali Baba's cave where one can find enormous troves of innovative data and original hypotheses. It is also a challenge for clinicians, nutritionists and public health experts when it comes to formulating dietary recommendations. When doing so, one should keep in mind that a well-designed scientific study addresses one specific question at a time. Given the numerous questions to be addressed, and the large amount of data available, conclusions should rest on the careful and objective meta-analysis of studies addressing the same questions.

In this overheated debate, it is essential that members of the scientific community have a clear understanding of the modern science related to added sugars and health.

So where does the modern science on sugar consumption and health effects really lie?

The articles in this supplement are based on presentations made at the European Congress on Obesity on 7 May 2015 entitled 'Sweeteners and Health: Findings from Recent Research and their impact on Obesity and Related Metabolic Conditions'. The intent of this symposium, and indeed of the five articles in the supplement, is to provide a review of modern science on the

metabolic and physiologic effects of fructose-containing sugars and their implications for various health-related conditions.

The first article of the symposium by Campos and Tappy in this issue delves into issues how fructose and glucose are metabolized and how this metabolism may influence their health effects. Campos and Tappy provide a historical prospective of the failure of previous attempts to stigmatize individual ingredients and their impact on various chronic conditions. They note that most cells in the human body do not directly use fructose and that virtually all of the fructose ingested is metabolized in the liver to glucose, glycogen, lactate or carbon dioxide. Campos and Tappy conclude that there are a few markers for harm when fructose-containing sugars are consumed as part of an isocaloric diet. They caution that while consuming large amounts of sucrose may increase triglycerides, the signal for harm does not occur until over 30% of energy is consumed as fructose, which almost double the 95th percentile of human consumption. They conclude that 'over-consumption of energy from all sources is much more important with respect to weight gain than the isolation of one element of the diet'.

The article by Rippe and Angelopoulos in this issue explores recently completed, randomized controlled trials and prospective cohort studies exploring potential linkages between sugars and risk factors for obesity, diabetes and heart disease. While cautioning that it appears prudent to avoid excessive consumption of fructose-containing sugars, Rippe and Angelopoulos report that levels within the normal range of human consumption, if substituted isocalorically in diets for other carbohydrates, do not appear to cause a unique risk for any of these conditions. The authors conclude that 'an undue focus on fructose-containing sugars may distract further research and public policy issues related to reduction of established risk factors for these three chronic metabolically based conditions'.

In the third article in this issue Benton and Young provide an in-depth look at the relationship between sugar consumption and food intake behavior. In particular, Benton and Young provides an in-depth look at the dopaminergic reward pathways that have been imputed to be stimulated by both drugs of abuse and sugar. They point out that multiple visual and behavioral stimuli also stimulate the reward pathways. They describe the danger of over-interpreting functional magnetic resonance imaging and also the significant limitations of extrapolating from animal data to human behavior. Benton and Young draw multiple distinctions between responses to drugs of abuse and sugar consumption and how they differ in their influence on the dopamine pathway. They conclude with an examination of numerous studies, none of which support the 'sugar addiction' hypothesis, and concludes that there is no evidence that sugar induces addiction in humans.

In the final article in this issue, Tappy offers a novel explanation for the role of sugar in the human diet throughout history. He reminds us that hunter-gatherers sought areas where fruits and berries were abundant to fuel themselves for their hunting activities. It was only many millennia later that agriculture made such crops readily available in multiple places around the world. Tappy reminds us that while sugar is increasingly presented as a 'non-essential nutrient', it was not only likely a major carbohydrate for hunter-gatherers but also in many parts of the world it remains an indispensable nutrient for many populations. Tappy reminds us that the human genome changes very minimally over thousands of years and proposes that it is 'non-genetic, hereditary material', which has changed the role of sugars in the developed countries. He concludes 'it appears premature to recommend a drastic reduction of sugar consumption in the general population when sugar presently contributes a substantial portion of world's food energy production'.

Issues related to added sugars and health carry important public health and policy questions. Indeed, scientific organizations such as the World Health Organization,[36] the Scientific Advisory Committee on Nutrition in England,[37] the American Heart Association[38] and the Dietary Guidelines Advisory Committee 2015[(ref. 61)] have all recently recommended significant reductions in added sugar to no more than 10% of energy in the diet. These guidelines are in contrast to the upper limit of 25% of energy previously set by the Institute of Medicine carbohydrate report[62] and by the European Food Safety Agency.[63]

The overall aim of this symposium is neither to stigmatize sugars as toxic nutrients nor to pretend that sugar is devoid of any adverse effects. Here, we believe that common sense should be combined with good science. We know for sure that obesity is related to an energy intake chronically exceeding energy requirements. We also know quite well that sugars make up to 15–20% total energy intake on average in most countries where obesity is highly prevalent. It is, therefore, undisputable that sugars, as a calorically dense part of our diet, contribute to obesity. It is also undisputable that sugar reduction (together with reduction of other energy-dense foods) should be part of any weight loss program. One should be very careful not to conclude that it is the one deleterious nutrient! All macronutrients contribute to total energy intake, and concluding that sugar is obesogenic, but not fat or complex starch, would be like pretending that, when eating a mix of candies of different colors, only the green ones make you fat! One should also keep in mind that scientists bear a wide responsibility toward the society that generally supports their research. Part of this responsibility is to have rock-solid evidence when it comes to issue recommendations that may have unexpected long-term impacts. Recommendation to decrease sugar intake, and possible litigations resulting from these recommendations, can be medically and ethically accepted only when there is strong evidence that sugars exert deleterious effects on health independent of excess energy intake. This implies that an upper level of intake should be identified (NB: IOM and EFSA concluded, based on a careful review of the literature, that such an upper limit level could not be identified). Furthermore, 'cut down sugar!' is no dietary recommendation! It should come with information on which nutrients should be substituted for sugar. This brings out other important questions that remain presently unanswered. Oversimplifying the issue by saying that sugar need not be replaced given the high prevalence of obesity is close to an insult to the many places in the world where undernutrition is still prevalent! It disregards the fact that feeding the planet becomes the major issue for future nutritionists, and that sugar production nowadays represents a substantial portion of food energy worldwide.

It is our hope that information contained in the articles in this supplement, together with emerging research from many laboratories around the world, will provide clarity, which will guide not only individuals' nutritional choices but also public health and public policy concerning the relationship between fructose-containing sugars and health.

It is only through sound scientific evidence that correct individual and public policy decisions in the area of nutrition and health can be made and guidance issued.

CONFLICT OF INTEREST

JM Rippe's research laboratory has received unrestricted grants and Dr Rippe has received consulting fees from ConAgra Foods, Kraft Foods, Florida, Department of Citrus, PepsiCo International, The Coca Cola Company, Dr Pepper Snapple Group, Corn Refiners Association and Weight Watchers International as well as royalties and editorial office support from CRC Press, Sage Publishing and Springer Publishers. LT has received lecture fees from Rippe Lifestyle Institute and Soremartec. LT has also received grant support from Swiss National Foundation for Science and Federal Office for Sport BASPO, Switzerland and serves as an expert witness for the French food security agency ANSES.

ACKNOWLEDGEMENTS

This article is based on a symposium entitled 'Sweeteners and Health: Findings from Recent Research and their Impact on Obesity and Related Metabolic Conditions' presented at the European Congress on Obesity on 7 May 2015 with sponsorship from Rippe Lifestyle Institute.

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