Could low-calorie sweeteners be contributing to the diabetes epidemic?

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Low-calorie sweeteners are often recommended to help lower total calorie intake or to help manage blood glucose levels in diabetics and those with glucose intolerance. Furthermore, low-calorie sweeteners are commonly used and consumed as tabletop sweeteners and as replacements for added sugars in manufactured products, helping towards producing alternative products and improving choice for the consumer. The safety of low-calorie sweeteners has been intensely investigated and reviewed over the past few decades and recent reevaluations of pre-approved low-calorie sweeteners have deemed their consumption, within specified intake levels, to be safe. However, recent research by Suez *et al.* (2014) entitled 'Artificial sweeteners induce glucose intolerance by altering the gut microbiota' has again ignited interest into the safety of low-calorie sweeteners. The research prompted media headlines including 'Artificial food sweeteners linked to diabetes' (*Daily Express* 2014), 'Sweeteners could cause obesity scientists warn' (*The Telegraph* 2014) and 'Study raises doubts over sweeteners' (*The Times* 2014). This is likely to have caused confusion among low-calorie sweetener consumers, especially as there are concurrent health messages to reduce the intake of 'added sugars'.

The research behind these headlines was predominately carried out in mice, starting with experiments that supplemented the rodents' drinking water with commercially available low-calorie sweeteners, namely saccharin, sucralose or aspartame (Suez *et al.* 2014). After 11 weeks, the glucose tolerance (a marker of diabetes risk) of the mice consuming water supplemented with commercially available low-calorie sweeteners (10% solution) was impaired compared with mice consuming the control drinks of either water or water supplemented with glucose or sucrose. Saccharin demonstrated the largest effect on glucose tolerance and, therefore, was subjected to further investigation. Accordingly, commercial

saccharin and pure saccharin, at an estimated pre-calculated dose of 5 mg/kg bodyweight per day for 11 weeks, were found to impair glucose tolerance in both lean and obese mice, compared with mice consuming glucose or water control drinks. The dose of pure saccharin was equivalent to the Food and Drug Administration (FDA) maximal acceptable daily intake (ADI) for humans (adjusted to the bodyweights of the mice). However, it is worth noting that this dose may well have a different effect in mice compared with humans because of the biological differences among species. The authors suggested that the observed effect caused by the saccharin may be mediated by changes in the gut microbiota of the mice because antibiotic treatment, which decreases the density of intestinal bacteria, resulted in glucose tolerance profiles that were comparable with the control groups. Furthermore, transferring the gut microflora from mice consuming the commercial saccharin to germ-free mice (bred in aseptic conditions to prevent gut microflora development) led to impaired glucose tolerance, compared with germ-free mice receiving microbiota from control mice consuming glucose. Sequencing of the faecal microflora 16S ribosomal RNA (rRNA), which indicates the microbiota composition, showed possible differences in the relative abundance of some bacterial taxonomic groups between mice consuming saccharin and those consuming the controls. Therefore, the authors suggest the saccharin may be modulating the microbe taxonomic entities residing in the guts of the mice. In addition, metagenomic sequencing and mapping of faecal samples collected from the mice consuming commercial saccharin suggests the enhancement of pathways involved in glycan degradation, compared with control mice consuming glucose. Suez and colleagues postulate that the enhancement of these pathways may lead to increased energy harvest and *de novo* glucose and lipid synthesis in the host. Pathways involved in the metabolism of starch, sucrose, fructose and mannose, and the biosynthesis of folate, glycerolipids and fatty acids were also enhanced in the microbiomes of the mice consuming commercial saccharin, compared with control mice consuming glucose. Similar pathways have been shown to be enhanced in the

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gut microbiota of type 2 diabetics and overweight individuals but this does not demonstrate causation. Therefore, the mechanism behind the observed impairment of glucose tolerance in the mice consuming saccharin requires further exploration. This seemingly expansive rodent study, which has its limitations with regard to the conclusions that can be drawn, was then followed by pilot investigations in humans.

A relatively small cross-sectional study that examined the relationship between long-term low-calorie sweetener consumption (assessed by a food frequency questionnaire) and clinical parameters related to metabolic syndrome in 381 non-diabetic participants, found significant positive correlations between low-calorie sweetener consumption and measures of bodyweight and glucose tolerance. However, this finding may be a result of reverse causation, as individuals may consume low-calorie sweeteners to help reduce bodyweight and/or risk of type 2 diabetes. The gut microflora 16S rRNA was characterised in 172 participants and significant positive correlations between taxonomic entities (including the *Enterobacteriaceae* family, the Deltaproteobacteria class and the Actinobacteria phylum) and low-calorie sweetener consumption were found. However, it is unclear whether this was due to the consumption of low-calorie sweeteners or another dietary or lifestyle factor associated with their consumption. To follow this up, seven healthy participants who did not normally consume low-calorie sweeteners were given commercial saccharin at the FDA ADI (5 mg/kg bodyweight) for 5 days. This underpowered and uncontrolled study showed that 4 out 7 participants had a reduction in glucose tolerance at the end of the treatment period compared with baseline and as such were termed 'responders' by the investigators. Bodyweight change was not investigated in this short-term study. Among these 'responders' the faecal microflora composition was found to be altered after consumption of saccharin compared with baseline and appeared to cluster differently from the 'non-responders' both before and after the consumption of saccharin. In addition, transfer of faecal samples, collected from the 'responders' post-saccharin consumption, to germ-free mice resulted in impaired glucose tolerance in the mice compared with mice who received faecal samples collected from the 'responders' before saccharin consumption. The authors concluded that the results of these experiments suggest that saccharin, at the levels consumed (maximal ADI), reduced glucose tolerance through modulation of the gut microbiota. However, these studies were not without their limitations, which reduce the transferability of the results to the general population.

Unfortunately, the study authors and resulting media coverage have generalised these findings to all low-calorie sweeteners. The initial rodent experiment was the only experiment to include the three low-calorie sweeteners (saccharin, sucralose and aspartame). Within this experiment, the data for the groups of mice receiving each low-calorie sweetener were combined together for statistical comparison with the data from the combined control groups (water, sucrose and glucose) and a significantly lower glucose tolerance in the combined low-calorie sweetener group was found. However, it appears the difference in glucose tolerance was primarily driven by saccharin, with negligible differences being found for one of the most commonly consumed low-calorie sweeteners in the UK, aspartame. Furthermore, the chemistry and metabolism of different low-calorie sweeteners can be quite diverse, with the only common feature being the provision of sweet taste. For example, the low-calorie sweetener aspartame is completely metabolised into amino acids and methanol, which are absorbed in the small intestine and so does not reach the large intestine (Butchko *et al.* 2002), whereas although sucralose does reach the large intestine, studies have shown that it cannot be metabolised by the gut microflora (Roberts *et al.* 2000). Therefore, generalising the findings of this study to include all low-calorie sweeteners is highly inappropriate. In addition, translating the changes in mice or human microbiota to health effects in humans is extremely complex. The consequence of the microbiota changes observed within this study to human health and whether these changes are sustained over medium- or long-term saccharin exposure remains unknown.

Moreover, although animal studies can prove useful in generating theories or designing experiments that cannot be performed in humans, the different biological processes in animals compared with humans means that the results obtained cannot be generalised to humans. Furthermore, even though the experimental human study was set out to help address this, it was severely underpowered, uncontrolled and of short duration. The cross-sectional human study was also relatively small, involving only 381 participants. Indeed, a recent large case cohort study, involving more than a quarter of a million people, showed no association between consumption of low-calorie sweeteners and incidence of type 2 diabetes (Romaguera *et al.* 2013). Moreover, as the experimental human study that involved only seven participants did not have a control group, a specific cause and effect relationship could not be established. In addition, separating 'responders' from 'non-responders' is likely to have occurred during *post hoc* analysis, and

the lack of reporting from the whole group analysis can only lead the reader to assume that no significant results were found. Furthermore, even within the 'responders' group, huge inter-individual variation in glycaemic responses was evident, meaning that other factors were likely to have been involved. Indeed, other dietary or lifestyle factors were not considered during the analysis of the study results and only a small part of the observational study, in which the relationship between glycosylated haemoglobin and the consumption of low-calorie sweeteners was analysed, corrected for BMI. In addition, the saccharin dose given in both the rodent and experimental human study equated to the FDA ADI (equivalent to 250 individual portion packets of table-top sweetener for the average adult), a level which is highly unlikely to be consumed, even for those regarded as high consumers of saccharin (FDA 2014). Moreover, blends of saccharin with other low-calorie sweeteners are most often used within the food and drink industry, to help deliver the best flavour profile. Therefore, investigations into low-calorie sweeteners, at the doses and blends commonly consumed, would be more applicable to the general population.

The safety of low-calorie sweeteners has been extensively scrutinised over the past couple of decades. Several reevaluations have been performed by risk assessment authorities including the FDA in the US and the European Food Safety Authority (EFSA), which have deemed sucralose, saccharin and aspartame to be of no safety concern at intakes below the specified ADI levels (Scientific Committee on Food 2000; EFSA 2013; FDA 2014). Furthermore, there is a strong body of evidence contradicting the findings of the study by Suez *et al*. A recent meta-analysis of 15 randomised controlled trials that investigated the substitution of added sugars with low-calorie sweeteners found beneficial effects on bodyweight (Miller & Perez 2014), which contradicts what was observed in the small cross-sectional human study. A review of the existing evidence investigating low-calorie sweeteners and metabolic disorders also found beneficial effects and concluded that the replacement of 'added sugars' with low-calorie sweeteners (which is associated with energy reduction) may help to reduce the risk of type 2 diabetes (Raben & Richelsen 2012), again contradicting what was suggested in both the animal and human studies.

On average, the UK population currently exceeds the recommended maximum intake level for 'added sugars' and for some individuals, substituting 'added sugars' with low-calorie sweeteners may help towards meeting these recommendations. Furthermore, low-calorie sweeteners may help to reduce calorie intake and so reduce the risk of obesity and type 2 diabetes. In conclusion, although emerging evidence from rodent studies is of interest, the current study does not provide convincing evidence that low-calorie sweeteners can impair glucose tolerance or increase the risk of obesity in humans. Larger randomised controlled human trials using realistic doses are required before any conclusions can be made.

Conflict of interest

The author has no conflict of interest to disclose.

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