Artificial sweeteners and glucose intolerance: a dietitians’ perspective

Leonie Garden, Kim Paterson

Suez et al. recently suggested that non-caloric artificial sweeteners (NAS) such as saccharin, sucralose and aspartame drive the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota. This research, as published in Nature,1 has attracted an abundance of media and health professional attention.

NAS are synthetic substitutes for sugar which pass through the human gastrointestinal tract without being digested; therefore they are widely used in the weight loss and diabetes industries.2 Since their introduction over a century ago there has been much controversy around these additives. Research has been conflicting, with large bodies of evidence for and against their use. The above proposal that NAS can induce glucose intolerance would make them inappropriate for the very people for whom they were intended, and may have a significant impact on the advice we give to these individuals in the future.

Current guidelines for the use of NAS

Non-nutritive or non-caloric ‘artificial’ sweeteners undergo a rigorous approval process and, if deemed safe for use, an acceptable daily intake (ADI) level is set. This is calculated to be 100 times less than the minimum amount that may cause health concerns, making over-consumption exceptionally difficult.3

Aspartame, sucralose and saccharin are considered safe for human consumption in moderation, classed as equal to or below the ADI. The ADI for each sweetener is 40, 0–15 and 0–5mg/kg body weight, respectively.4

The use of non-nutritive sweeteners in place of nutritive sweeteners such as sugar is currently recommended as a way of reducing overall carbohydrate and caloric intake. Those with diabetes and obese/overweight individuals will often use NAS as a tool for glycaemic control and weight loss. The health-conscious population may use these to reduce their risk of weight gain and metabolic disease.3

NAS consumption in mice

Conflicting studies prompted researchers from the魏兹曼研究所,以色列, to further investigate the effect of NAS on both mice and humans. They conducted several experiments initially in mice and later in humans. The first experiment involved giving lean mice commercial formulations of NAS (saccharin, sucralose and aspartame) in drinking water compared with mice given water alone or water with added glucose. Results showed that NAS-consuming mice developed clear glucose intolerance, with saccharin having the most profound effect. Subsequent studies looked into the effect of both pure and commercial saccharin versus glucose, on mice being fed 60% energy from fat to represent an obese population. Both types of saccharin were associated with impaired glucose tolerance.

NAS are not absorbed or digested by the body but come into direct contact with the intestinal microbiota which have a variety of physiological functions and impact on our health. Researchers treated the mice with antibiotics to deplete their intestinal microbiota while continuing to feed them saccharin, investigating the hypothesis that this may be responsible for the observed glucose intolerance. After four weeks of antibiotic treatment there was no difference in glucose intolerance between NAS-drinking mice and controls, in both lean and obese populations.

The next phase of the experiment involved transferring the microbiota from both groups of mice into germ-free recipients via faecal transplantation. Recipients of microbiota from mice consuming commercial saccharin exhibited impaired glucose tolerance as compared with mice transplanted with microbiota from the control group. These results indicate that NAS consumption alters intestinal microbiota which in turn could facilitate metabolic derangements such as glucose intolerance.

Research in animals is frequently one of the first steps employed to investigate theories regarding the biological outcomes of substances. While helpful, these studies may not reflect what happens in humans and therefore we must exercise caution when using theories taken from this type of research in clinical practice.

NAS consumption in humans

After completing several studies in mice, research was extended to the effect of NAS in humans. Long-term NAS consumption was assessed via a food frequency questionnaire in 381 non-diabetic individuals. Significant positive correlation was found between NAS consumption and metabolic syndrome related clinical parameters such as increased weight, and waist to hip ratio, higher fasting blood glucose and HbA1c levels.

Further to this the researchers recruited seven non-diabetic individuals who did not usually consume NAS. Over six days the participants consumed the FDA’s maximum daily intake of commercial saccharin. Participants underwent continuous glucose measurements and daily glucose tolerance tests. Four out of the seven developed significantly poorer glycaemic responses five to seven days after NAS consumption. When analysed, the microbiota of these four participants underwent pronounced compositional changes. However, it must be noted that at the start of the study week there was a difference in microbiota configurations between the four participants who responded and the three who did not.1

Published research has suggested that the modern ‘Western’ diet (high fat/high sugar) has led to a change in genetic composition and metabolism of the human
gut microbiota. It has been hypothesised that these alterations are contributing to growing rates of chronic illness in the developed world.\(^7\)

**Limitations**

Research conducted in mice has given rise to major developments in our capability to treat many life-threatening diseases and conditions. Ninety-nine percent of genes found in mice have an equivalent gene in humans, and therefore they are thought to be valuable when studying the prevention and treatment of diseases, including cancer, cardiovascular diseases and diabetes. The use of larger animals such as dogs, pigs and non-human primates in research is considered inappropriate due to extensive costs and ethical concerns despite them being more closely related to humans. When applying data gathered from animal research to humans and disease we must consider the problems of extrapolation. Despite a close genetic link between species, there will still be significant differences would influence human studies.\(^7\)

Erroneous or inadequate information. Using animals also eliminates the effects of lifestyle factors which influence human studies.\(^7\)

The results gathered from the human component of the study by Suez et al.\(^1\) should be considered with caution. It consisted of only seven participants, too few from which to draw any sound conclusions. The study results actually suggest that individuals have a personalised response to NAS stemming from differences in microbiota observed prior to study intervention, meaning the glycaemic effects described may only apply to certain individuals.

A major challenge when looking at the effect of specific dietary components on health and disease is obtaining accurate information on nutrient intakes. Food frequency questionnaires, such as those used in Suez et al.’s study,\(^1\) are designed to assess habitual diet by asking about the frequency with which food items or specific food groups are consumed over a reference period. They cannot be depended upon to provide reliable estimates of absolute intake. Foods perceived as healthy, such as fruit and vegetables, are commonly over-reported with consumption seen as unhealthy, such as full sugar drinks, being under-reported. The latter example could affect the results of a study such as the one being discussed.\(^5\)

**Other literature**

A consensus statement published in December 2014 outlines the beneficial role of NAS. The authors agree that a desirable effect on postprandial blood glucose levels is observed in both diabetic and non-diabetic individuals consuming NAS. It should be noted, however, that this piece of work was fully funded by the International Sweeteners Association.\(^9\)

A small study carried out in 2014 year found that there was no additional glycaemic response observed when NAS were consumed along with glucose. However, Accesulfame-K exerted a slight effect and requires further investigation.\(^10\)

Grotz et al. carried out a study on 128 individuals with type 2 diabetes. Participants were given sucralose (at doses of 7.5 mg/kg/day) or a placebo for a period of three months and results showed that sucralose had no effect on glucose homeostasis.\(^11\) Ma et al. studied the effect of sucralose on 10 non-diabetic subjects. They were given an intraduodenal solution of sucrose or saline, both later followed by glucose. Sucralose was shown not to enhance the absorption of glucose from the small intestine, or increase blood glucose levels or plasma GLP-1 concentrations.\(^12\)

In 2010, Anton et al. carried out the first study directly examining the effects of the natural sweetener, stevia, on food intake, satiety, and postprandial glucose and insulin levels in non-diabetic humans.\(^5\) Participants were given a pre-meal snack sweetened with NAS (stevia or aspartame) or sucrose. It was found that consumption of stevia significantly lowered postprandial insulin levels compared to both aspartame and sucrose. Both the aspartame and stevia groups showed a reduction in postprandial glucose compared to sucrose. The effects exhibited on postprandial glucose levels are likely due to the lower caloric and carbohydrate intake in the aspartame and stevia snacks compared to the sucrose snacks (290 kcal versus 490 kcal). A positive outcome was that participants did not compensate by eating more at meal times when they consumed lower calorie snacks containing stevia or aspartame compared to when they consumed higher calorie snacks containing sucrose.\(^13\) However, other authors have suggested this is not the case, and that the use of NAS (in particular from diet drinks) may result in increased body weight and metabolic abnormalities. It is suggested that drinking diet drinks may increase the craving for and consumption of high sugar, energy dense food and drink, or may cause the consumer to underestimate their energy intake and result in a positive energy balance leading to weight gain.\(^14\)

From the above we can see that individual sweeteners may exert slightly different effects. The article which appeared in *Nature* focused on saccharin, but the results were portrayed by the media to apply to all NAS.

**Conclusion: is it time to change?**

The study by Suez et al.\(^1\) suggests that NAS can cause metabolic derangements with a link to changes in gut microbiota. At this stage it is uncertain how NAS are exerting this effect. This study has sparked interest in the area of NAS and glucose intolerance, and has provided a platform for further research. In light of this research many dietitians, endocrinologists and diabetes specialist nurses have taken the time to reflect on their current practice and consider potential radical changes in their recommendations.

One study, carried out predominantly in animals, does not provide sufficient evidence to warrant changes in clinical practice. Further studies incorporating larger numbers of participants (healthy weight, obese or diabetic, non-diabetic) consuming more realistic amounts of artificial sweeteners are needed. This would provide more solid confirmation of the link between NAS and...
glycaemic control. In a world where obesity and diabetes are on the increase, we as health professionals need to be more proactive and this area is certainly one to watch.

Until a time when more evidence is available, health professionals should continue to encourage a diet low in sugar with a moderate amount of NAS if the individual wishes to consume these products.

**Leonie Garden**, Diabetes Specialist Dietitian, The James Cook University Hospital, Middlesbrough, UK

**Kim Paterson**, Diabetes Specialist Dietitian, Friarage Hospital, Northallerton, UK

**Declaration of interests**

There are no conflicts of interest declared.

**References**


**POEMS**

**Clinical question**

Does intensive glycaemic control in high-risk patients with type 2 diabetes decrease the frequency of ischaemic heart disease events?

**Bottom line**

Intensive glycaemic control compared with usual care doesn’t reduce the rate of ischaemic heart disease events. As demonstrated in multiple studies, an elevated glucose level in a patient with type 2 diabetes is a risk factor for bad outcomes, but lowering the glucose level does nothing meaningful other than lowering the glucose level.

**Reference**


**Synopsis**

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial randomised more than 10 000 men and women aged 40–79 years with type 2 diabetes and known cardiovascular disease, or cardiovascular risk factors, to either intensive glucose control (glycated haemoglobin target: <6.0%) or usual control (target: 7.0–7.9%).

The intensive control part of the trial, although demonstrating a decrease in the rate on non-fatal myocardial infarctions, was terminated early because of excess mortality in the patients assigned to intensive control. The study team decided to continue following the patients for the remainder of the study period. So this becomes a difficult design to evaluate – for the first 3.7 years, some patients received intensive treatment and some received usual care, but for the last 18 months of the study, everybody was treated the same. This is probably best considered as a secondary analysis of the ACCORD trial and therefore better at generating hypotheses than answering them. Nonetheless, the authors report slight reductions in the rate of the combined outcome of myocardial infarction, revascularisation, and unstable angina; when adjusting for glycated haemoglobin concentration over time, however, all differences went away. Since the original study was a major downer for the ACCORD team and for those who still want to promote tight glycaemic control in patients with type 2 diabetes, these authors report on a secondary analysis of what happened after the intensive treatment was halted.

In other words, this was really a thinly disguised attempt to salvage something out of the failed ACCORD trial. The only thing they found has already been demonstrated in too many studies to count: an elevated glucose level in a patient with type 2 diabetes is a risk factor for bad outcomes, but lowering the glucose level does nothing other than lowering the glucose level.