Effects Of Non-Nutritive Sweeteners on Obesity, Type 2 Diabetes and Other Metabolic Health Problems

Wenya Gao

University of Leeds, Leeds, West Yorkshire, LS2 9JT, The United Kingdom

*Corresponding author: fs21wg@leeds.ac.uk

Keywords: Obesity, Type 2 Diabetes, Metabolic Health Problems, Diet drink, Non-Nutritive Sweeteners.

Abstract: Nowadays, metabolic health problems such as obesity or diabetes are more and more common in people. Many people hope to improve or prevent these metabolic health problems by replacing sugar-sweetened beverage (SSB) and sugar with Diet drink and non-nutritive sweeteners (NNS). With the increasing consumption of diet drink and NNS, more and more researchers have begun to study their effects on metabolic problems. Some prospective studies suggest that consumption of NNS may affect the balance of gut microbes and thus affect metabolic health problems, also possibly lead to obesity or glucose metabolism problems. This paper reviews relevant studies and concludes that NNS does affect intestinal microbial balance in animal and cell experiments, but further research is needed in other directions. To study the mechanism of NNS affecting metabolic health, the experimental conditions were needed and randomized trials need to added. This will be the direction of further efforts.

1. Introduction

Metabolic health problems are associated with many factors, such as several cardiovascular risk factors associated with insulin resistance. Obesity, high blood sugar, high blood pressure are all possible causes of metabolic abnormalities. And the incidence of these chronic diseases is rising all over the world. These diseases are no longer diseases of the rich. A global shift in illness patterns has been seen, with infectious diseases having a declining relative impact and chronic diseases such as cardiovascular disease, cancer, and diabetes progressively dominating disease patterns. There is no denying that more scientific research is needed to prevent these diseases.

A number of prospective studies have linked NNS and diet drinks containing artificial sweeteners to metabolic health problems. The goal of this paper was to look at the existing findings on the association between NNS and Diet drink consumption and the risk of obesity, type 2 diabetes (T2D), and metabolic disease. The studies included in the evaluation were mainly controlled trials and observational studies. The scientific literature has debated theories and mechanisms as to whether NNS and diet beverages prevent or increase the risk of obesity, T2D and metabolic disease.

2. Effects of NNS on metabolic health

2.1 Mechanisms by which NNS affect gut microbes

Many prospective studies suggest that long-term use of NNS affects human metabolic health. There is now growing evidence that NNS can affect the gut microbes. The gut microbiome is made up of a variety of bacteria, but the main bacteria include: firmicutes, the phyla Bacteroidetes, actinobacteria and proteobacteria. The gut microbes play a key role in metabolism and other human mechanisms. The following studies are designed to support this view.

A number of recent research has shown that gut microbes play a role in the metabolic health of the host. In 2010, Velagapudi et al. found that Angptl 4 is related to gut microbes. Gut microbes can enhance the extraction of triglycerides by inhibiting Angptl 4. And facilitate the storage of adipose

  DOI: 10.25236/gemfe.2022.007

tissue [1]. 2014 Mattijssen, F. Further non-study of Angptl 4 found that it can increase body weight by reducing its inhibitory effect on lipase [2]. The specific situation is shown in Figure 1 [3].

This graphic summarizes how gut microbes affect metabolic health through four distinct mechanisms. The first way: gut microbes reduce AMPK activity in liver, adipose tissue and muscle and affect free fatty acid oxidation leading to obesity. The second way: gut microbes reduce the content of ANGPTL 4 in the gut, resulting in decreased LIPASE activity in the gut, affecting lipid absorption and leading to obesity. The third way: gut microbes can increase the fermentation of complex carbohydrates, turning complex carbohydrates into monosaccharides and increasing energy absorption leading to obesity. In addition, the absorption of monosaccharides has a certain chance of causing fat growth in the liver to affect the probability of obesity.

In 2018, Wang et al. conducted a study on the effects of different NNS on gut microbes. In this research they studied the Sucralose, Saccharin, Acesulfame potassium (Ace-k) and Rebaudioside A four kinds of NNS separately. In cell experiments by performing liquid culture assays or LB agar plate assays for different NNS. The results show that sucralose has antibacterial effect on Escherichia coli. Data analysis showed that the quantity of colonies present on LB agar plates was reduced by 30% and 74% and the colony size was reduced by 22% and 77% at 1.25% and 2.5% sucralose solutions, respectively [4].

Studies on Ace-k (2.5% w/v) and saccharin (2.5% w/v) found that they significantly inhibited the growth of E. coli HB101 by 90% and 98% and E. coli K-12 by 98% and 99.5%, which is show in Figure 2 [4]. However, sucrose and NaCl in LB medium did not affect bacterial growth.

An interesting phenomenon occurred when studying the effect of 2.5% concentration of Rebaudioside A on E. coli, the colony number of E. coli HB101 was reduced by 83% but that of E. coli K-12 was not affected. Therefore, it is concluded that Rebaudioside A has a selective inhibitory effect on different intestinal flora.

After finding that NNS has bacteriostatic effect in vitro, Wang et al. began to conduct animal experiments. Two groups of mice with different dietary patterns (chow diet and high fat diet) were investigated in the presence or absence of a solution of 2.5% (w/v) sucralose. Found that Sucralose affect the gut microbiota of young mice. Changes in the gut microbiome of mice were detected by 16s rDNA detection of mouse feces. Compare to chow diet mice, the group with sucralose have a decreased trend in Bacteroidetes, however sucralose have no effect on actinobacteria and proteobacteria in chow diet group. Bifidobacterium was significantly increased when adding sucralose.

In high fat diet sucralose have no effect on clostridium and bifidobacterium. And sucralose show a long-lasting increase in firmicutes and decrease in Bacteroidetes species.

Wang et al. study the effects of sucralose on major gut microbes in mice. And proved that sucralose in the short term affects the growth of intestinal microbes and changes intestinal balance. However, further human trials are required to establish the effect of sucralose on the human gut microbial balance.

Palmna et al. 2014 also found that the NNS aspartame has an effect on gut microbes. Changes in the microbial balance in the gut were analyzed using 16s rDNA assays in the feces of experimental mice. Experimental data showed that higher levels of Clostridium leptum were found when aspartame was added to both normal diet-fed and high-fat-fed mice. However, aspartame also attenuated the high-fat diet-induced increase in Clostridium Cluster XI [5].

A high-fat diet decreases Bacteroides while increasing Firmicutes. The addition of aspartame to a high-fat diet reduced the increase in Firmicutes but had no effect on Bacteroides.

On the one hand, aspartame led to an increase in propionic acid in both high-fat and normal diet feeding. This may be due to the increased production of Clostridium spp. which can lead to metabolites during oligosaccharide fermentation. Some species of this type of bacteria can break down carbohydrates to produce organic acids, such as propionic acid. There are other studies showing that NNS D-tagatose has been found by Laerke to increase the propionic acid content of the large intestine of pigs [6]. While propionic acid affects the immune system, colon motility and permeability, these affect the gut microbiome [7, 8].

On the other hand, the decomposition products of aspartame are not totally absorbed by the small intestines, and some of them will enter the colon and be fermented by the intestinal microbiome, affecting the intestinal microorganisms [9].

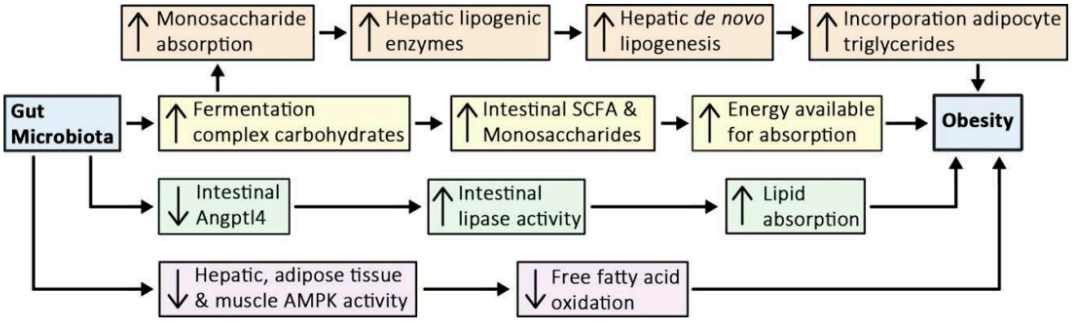

Figure 1. Mechanisms of gut microbes affecting obesity [3].

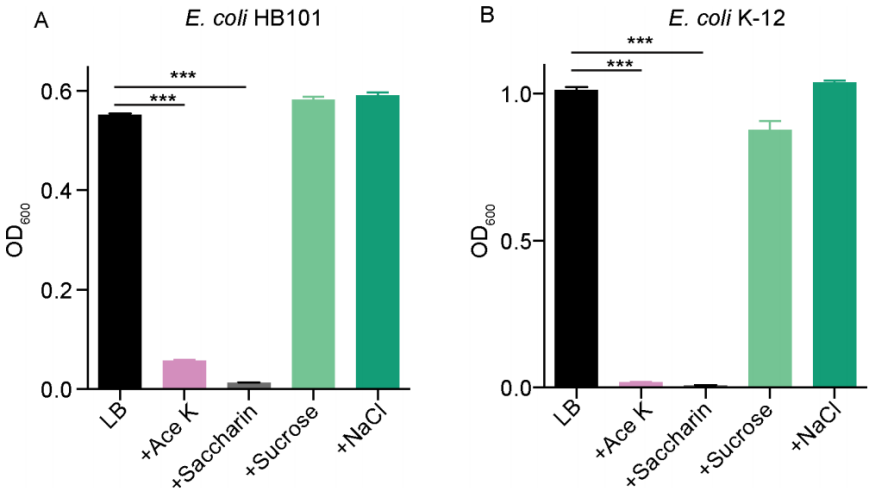

Figure 2. Ace K and saccharin show bacteriostatic effects on E. coli in vitro [4].

2.2 Effects of NNS on glucose intolerance

In 2014, Jotham Suez et al. studied the effects of saccharin on the gut microbiome. The in vitro culture method was used for the saccharin group as well as the control group. The relative taxonomic abundance for Bacteroidetes was found to be 89% in the saccharin group and 70% in the control group. And the relative taxonomic abundance for Firmicutes the saccharin group was 6% and the control group is 22% [10].

In the subsequent mouse experiments, in vivo culture of saccharin-added mice, in comparison to control group of germ-free mice, it was found that the germ-free mice in the control group had a higher tolerance to glucose in vivo.

Collectively, these results suggest that saccharin affects the composition of the microbiome and induces dysbiosis, the cause of host glucose intolerance.

The above studies have demonstrated the effects of sweeteners on gut microbes, and the effects of gut microbes on metabolic health, including obesity and glucose intolerance, using in vitro culture or animal experiments, and described the mechanisms of the effects. However, experimental evidence to demonstrate such effects and mechanisms in humans is still insufficient and further research is needed. This is the research direction that should strive for.

The sweetener Ace-k was studied by Jasmine et al. since many pregnant women in the United States also tend to use sweeteners in place of sugar, however, due to the uncertainty of sweeteners for metabolic health and the absence of clear limits for pregnant women. They were assessed by RT-PCR or histology using high fructose corn syrup and water as controls [11].

Experimental results show that Ace-k intake during pregnancy affects maternal glucose intolerance. Compared with the water group, the Ace-k group decreased the expression of transcription factors regulating glucose and lipid metabolism. This is related to metabolic diseases. Previous experiments have shown that sweeteners cause glucose intolerance by altering gut microbes, and this aspect can also be investigated as a possible mechanism.

Experimenters also observed hypoglycemia in newborn male, growth-restricted in newborn females, and these results suggest that metabolic problems in pregnant women who ingest Ace-k may be passed on to the fetus. However, whether metabolic problems persist long-term after subsequent fetal growth requires further study.

In 2013, Kimihiko et al. found the same view as the above study when they studied the effect of NNS on metabolism. Glucose tolerance was affected by NNS compared to the water control group [12].

Furthermore, NNS reduced the level of UCP1 in brown adipose tissue (BAT) compared with the water control group, but had no significant effect on markers of energy homeostasis in brain, liver and muscle. UCP1 is a class of UCPs called Uncoupling protein, which is expressed in BAT and when activated it leads to uncoupling of the respiratory chain and thermogenesis which involve energy balance. This result suggests that NNS may affect energy metabolism through UCP1.

After clarifying the effect of NNS on UCP1, it is essential to comprehend the method by which NNS reduces UCP1. In the results of Kimihiko's research, it was found that NNS has an increased effect on leptin levels, which indicates that there is leptin resistance in mice. In a previous study, Sell et al. found that leptin resistance reduces UCP1 levels. Therefore, the reduction of UCP1 by NNS found in the results may be due to the resistance of NNS to leptin [13].

However, there are other research experiments that show that NNS has a positive effect on weight control and metabolic health [14]. The reason for the inconsistency with the above experimental results may be due to different variables such as the type of NNS, experimental design, and experimental duration. A more complete experimental mechanism and more experimental groups are needed to reduce errors.

3. Effect of diet drink on T2D in human body

3.1 Background and information about diet drink

Diet drink is a common term for beverages sweetened with NNS or artificial sweeteners (ASB). Diet drinks are consumed at a much lower rate than SSB, and as ABS-containing drinks are mostly purchased for weight loss. A number of prospective studies have investigated whether ASB beverages actually help with weight loss, and whether the opposite cause-and-effect relationship exists, since overweight or obese people may choose ASB beverages as a result of trying to control their weight.

The following studies provide information on the effects of ASB on body weight and T2D. The following experiments were discussed to determine whether ASB affects weight gain and T2D, and whether it is reasonable to replace SSB with ASB. Whether there is reverse causality interfering with the experimental results.

3.2 Analysis of experimental results

Sakurai et al. 2013 studied the effect of diet sodas on the incidence of T2D. Diet sodas contain NNS. They took more than 2,000 men from a factory and asked them to keep track of their diet soda consumption. Diabetes was discovered after annual physical checkups over a seven-year span. According to research, diet soda consumption is associated with weight gain, possibly because the sweeteners in diet soda increase the brain's craving for food. Replacing SSB beverage with diet soda may not result in weight loss, but rather in excess energy intake due to appetite.27-30 There are still other confounding factors in the influence of diet soda on body weight and diabetes incidence, which requires further study to evaluate the influence of diet soda itself on weight gain and diabetes incidence [15].

Studies have shown that ASB and diet sodas increase GLP-1 secretion in people with type 1 diabetes and healthy controls, but have no effect on people with T2D. Despite the fact that diet soda is non-caloric and promotes incretin secretion, it cannot be utilized to prevent or treat diabetes.

The final results showed that there is a link between diet soda and diabetes in middle-aged Japanese men. (P for trend = 0.013) However, despite being a zero-calorie drink, diet soda is not always useful in preventing T2D.

The results of Laura et al. 's study are similar to those of the above study. In 2015, Laura et al. studied the effects of diet on T2D and obesity of SSB and ASB. Dietary assessment beverage intake was recorded for seven days. In the following 10.8 years, 847 cases of T2D were confirmed [16].

The study found an association between ASB intake and T2D, but found no association after controlling for obesity. This could be because people who are obese or overweight and at a heightened hazard for chronic diseases consume more ASB than those who are not [17]. And this is supported by evidence. Obesity is more prevalent among ASB consumers. Earlier studies that found no link between ASB and T2D add to the evidence that obesity is a confounding factor.

Overall research shows that consumption of SSB such as soft drinks and milk beverage is associated with a higher risk of T2D, drinks containing ASB intake did not reduce the incidence of T2D, and ASB alternative to soft drinks have no obvious effect on the incidence of T2D, the same number of calories to a drink instead of SSB does not change anything of real substance. Reducing consumption of SSB and promoting unsweetened coffee or tea as a diabetes-preventing alternative to SSB could help curb the escalating diabetes epidemic.

In addition, the same view was found in the research of Guy Fagherazzi et al. In 2013 the effects of ASB and SSB consumption on T2D mellitus were studied by them. ASB consumption was found to be positively associated with T2D risk in both age-adjusted and multivariable models [18]. However, in the absence of factors other than controlled ASB consumption, randomized trials are needed to demonstrate an association between ASB consumption and T2D.

A direct association between SSB and ASB and risk of T2D was found in a study of some French women, and the association persisted after adjusting for BMI and energy intake. Same support as the above research.

According to the findings of this investigation, the biological mechanisms leading to ASB and T2D remain unclear, and insulin can still be listed as a possible cause based on previous studies. For overweight or obesity, researchers found that ASBs was independent of the harmful effects of BMI. And the strength had a negative gradient of the association between ASB consumption and T2D risk across the entire BMI category, suggesting that ASB attenuates the negative effects of ASB consumption in women who are already overweight or obese.

To test whether the effect of ASB on T2D was due to reverse causality, follow-up analysis of the subjects found that although ASB consumption was more frequent in T2D patients. But when people have pre-diabetes, they also tend to use ASB rather than SSB. This suggests that the odds of reverse causality in the study are small.

There are some limitations to the study for future studies: eating habits can change over time. Even if the records of the subjects during the study were very detailed, there would still be changes in eating habits during the follow-up, resulting in inaccurate data. The type of ASB is also very important, and the type of ASB or SSB consumed by the study subjects should be recorded in more detail. Finally, when stratifying by BMI, there is low statistical power in several subcategories. As a result, stratified analysis, particularly of ASB consumption, should be interpreted cautiously.

In addition to the above supportive studies on ASB's influence on body weight and diabetes, there are other studies that have not found that ASB has a significant impact on T2D. Lawrence et al. investigated the relationship between ASB and T2D and concluded that ASB were not associated with T2D [19].

Participants who consumed ASB before the study began were found to be more likely to report weight gain or loss before the study began, to have tried a low-calorie diet, and to have a family history of chronic conditions such as T2D, which is linked to higher of T2D. After adjusting for these confounding factors throughout the study, ASB were no longer significantly associated with T2D.

While the study found no additional risk associated with substituting SSB for ASB, there is still controversy surrounding their use. Therefore, further research into the safety of ASB may be necessary.

The purpose above is to study the existing evidence on ASB research, explain the impact of ASB and whether there are experimental limitations. With the development of The Times and the progress of science, it is impossible to conclude the long-term effects of diet drinks on health based on tentative research results. More research is needed to elucidate its mechanisms and effects.

4. Conclusions

In the modern food environment, the addition of NNS to food and beverages has become increasingly common. Despite the fact that the extant literature on the biological implications of NNS, particularly in humans, is highly contentious, the above observational studies suggest an association between NNS intake and the development of metabolic disease and that NNS is not physiologically inert, but it also needs to be determined whether obesity is a confounder. Regarding the effect of different NNS on different gastrointestinal microbes, the effect of intestinal microbes on metabolic health, whether there is a reverse causal relationship, and the mechanism of the influence of diet drink on the incidence of T2D, it is still not fully understood. Conclusions about the effects of NNS on human health are drawn in the context of the current level of understanding. As science advances, further research should be conducted on the impact of NNS on human health and its limitations.

References

[1] Velagapudi V. R., Hezaveh R., Reigstad C. S., et al. The gut microbiota modulates host energy and lipid metabolism in mice [J]. J Lipid Res, 2010, 51(5): 1101-12.

[2] Mattijssen F., Alex S., Swarts H. J., et al. Angptl4 serves as an endogenous inhibitor of intestinal lipid digestion [J]. Mol Metab, 2014, 3(2): 135-44.

[3] Janssen A. W., Kersten S. The role of the gut microbiota in metabolic health [J]. Faseb j, 2015, 29(8): 3111-23.

[4] Wang Q. P., Browman D., Herzog H., et al. Non-nutritive sweeteners possess a bacteriostatic effect and alter gut microbiota in mice [J]. PLoS One, 2018, 13(7): e0199080.

[5] Palmnäs M. S., Cowan T. E., Bomhof M. R., et al. Low-dose aspartame consumption differentially affects gut microbiota-host metabolic interactions in the diet-induced obese rat [J]. PLoS One, 2014, 9(10): e109841.

[6] Laerke H. N., Jensen B. B. D-tagatose has low small intestinal digestibility but high large intestinal fermentability in pigs [J]. J Nutr, 1999, 129(5): 1002-9.

[7] Rahiman F.,Pool E. J. The in vitro effects of artificial and natural sweeteners on the immune system using whole blood culture assays [J]. J Immunoassay Immunochem, 2014, 35(1): 26-36.

[8] Tremaroli V., Bäckhed F. Functional interactions between the gut microbiota and host metabolism [J]. Nature, 2012, 489(7415): 242-9.

[9] Lipton W. E., Li Y. N., Younoszai M. K., et al. Intestinal absorption of aspartame decomposition products in adult rats [J]. Metabolism, 1991, 40(12): 1337-45.

[10] Suez J., Korem T., Zeevi D., et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota [J]. Nature, 2014, 514(7521): 181-6.

[11] Plows J. F., Morton-Jones J., Bridge-Comer P. E., et al. Consumption of the Artificial Sweetener Acesulfame Potassium throughout Pregnancy Induces Glucose Intolerance and Adipose Tissue Dysfunction in Mice [J]. J Nutr, 2020, 150(7): 1773-1781.

[12] Mitsutomi K., Masaki T., Shimasaki T., et al. Effects of a nonnutritive sweetener on body adiposity and energy metabolism in mice with diet-induced obesity [J]. Metabolism, 2014, 63(1): 69-78.

[13] Sell H., Deshaies Y., Richard D. The brown adipocyte: update on its metabolic role [J]. Int J Biochem Cell Biol, 2004, 36(11): 2098-104.

[14] Reyna N. Y., Cano C., Bermúdez V. J., et al. Sweeteners and beta-glucans improve metabolic and anthropometrics variables in well controlled type 2 diabetic patients [J]. Am J Ther, 2003, 10(6): 438-43.

[15] Sakurai M., Nakamura K., Miura K., et al. Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men [J]. Eur J Nutr, 2014, 53(1): 251-8.

[16] O'Connor L., Imamura F., Lentjes M. A., et al. Prospective associations and population impact of sweet beverage intake and type 2 diabetes, and effects of substitutions with alternative beverages [J]. Diabetologia, 2015, 58(7): 1474-83.

[17] Malik V. S., Hu F. B. Sweeteners and Risk of Obesity and Type 2 Diabetes: The Role of Sugar-Sweetened Beverages [J]. Curr Diab Rep, 2012.

[18] Fagherazzi G., Vilier A., Saes Sartorelli D., et al. Consumption of artificially and sugar-sweetened beverages and incident type 2 diabetes in the Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale-European Prospective Investigation into Cancer and Nutrition cohort [J]. Am J Clin Nutr, 2013, 97(3): 517-23.

[19] De Koning L., Malik V. S., Rimm E. B., et al. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men [J]. Am J Clin Nutr, 2011, 93(6): 1321-7.