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Sweeteners and Sugar- Their Impact on Human Metabolic Health and Chronic Diseases

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The rising global consumption of sugars and sweeteners has sparked significant concern over their impact on human metabolic health and chronic diseases. This paper reviews the role of various sugars and artificial sweeteners in contributing to health issues such as obesity, diabetes, cardiovascular diseases, and metabolic syndrome. Sugars, including glucose, fructose, and sucrose, are integral to the human diet, providing essential energy but also posing risks when consumed in excess. The research highlights that excessive sugar intake, particularly from processed foods, correlates with a heightened risk of chronic diseases, including diabetes and heart disease. Artificial sweeteners, while offering a low-calorie alternative, also carry potential health risks, such as carcinogenicity and metabolic disturbances. These sweeteners, including saccharin, aspartame, and sucralose, are extensively used in various food products, but their long-term effects remain a topic of debate. The paper underscores the importance of a balanced diet that limits the intake of added sugars and emphasizes the need for further research to fully understand the complex relationship between sugar consumption and chronic diseases. It suggests that natural sweeteners may offer a safer alternative, though more studies are needed to evaluate their effectiveness across different populations, particularly those with metabolic disorders. This review article aims to analyze the effects of sugars and artificial sweeteners on human metabolic health and chronic diseases, such as obesity, diabetes, and cardiovascular conditions. It emphasizes the need for balanced consumption and public health strategies to reduce added sugars and promote safer alternatives.

Keywords: Artificial Sweeteners; Chronic Diseases; Cardiovascular Diseases; Metabolic Health; Sugar Consumption.

The taste sense system is a major determinant of quality of life. We choose it mainly based on how much we value the experience of their flavour or how much we dislike it. Humans are one of the few creatures who prefer sweet flavours in a variety of intensities. By the sixteenth week of pregnancy, taste receptors begin to develop in the foetus, and the newborn baby can react favourably to solutions that have been sweetened.[1]The primary energy source in food is carbohydrate. Their structure and well-balanced taste, which is sweet in sugars make them noteworthy. Carbohydrates have two forms mainly complex molecules and simple carbohydrates which is also known as sugars. The primary dietary sources of sugars include fruit, some vegetables, milk, soft drinks, and confections. A sugar's structure is referred to as a monosaccharide. The mono-components include glucose, fructose, and galactose. Two monosaccharides combine to make a disaccharide.

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For instance, glucose and fructose together yield the disaccharide sucrose, also known as table sugar. Maltose is composed of two glucose molecules, while lactose is made up of one glucose molecule and one galactose molecule. All sugars have four calories per gram and are classified as carbs. Consumption of sugar in the diet on a daily basis is crucial. Sugars provide the brain with a quick source of glucose for cognitive muscles and functions.[2]

In processed foods, added sugar is added for sweetness, flavour enhancement, freezing or melting point modification, and food spoiling prevention. Natural foods are a better source of sugar because they also contain other micronutrients. These days, there are concerns about the potential link between diabetes or metabolic syndrome and high sugar intake, particularly in processed foods.[3] All forms of carbohydrates need to be included in a diet. The Food and Agriculture Organisation (FAO) and World Health Organisation (WHO) recommended that simple carbohydrates and sugars account for no more than 10% of total calorie consumption of a worthy diet. Sugars must be included in a balanced diet, with the consumption of sugar- sweetened beverages kept to a minimum. Additionally, it has been suggested that consumption of sweets or sugar-sweetened foods be restricted to no more than three times per day and no more than 6% of total caloric intake in order to get benefits.[4]

Human diets have included sugar from prehistoric times. China and India are said to have consumed the product first, followed by Europe following the crusades in the eleventh century. Many foods contain both added or extrinsic sugars, which are sugars and syrups added to foods and beverages during processing and preparation, and natural dietary sugars, such as lactose, sucrose and fructose. The United States has seen a sharp rise in sugar consumption during the previous three decades. The primary cause of this growth is the use of high fructose corn syrup (HFCS), which is currently consumed in excess of 62 pounds per person year, mostly in the form of sugar-sweetened beverages (SSB). Soft drinks, fruit drinks, energy and vitamin water drinks are included in SSB.[5]

Evidence suggests that sugars may have a negative impact on health. An increased risk of dental caries, obesity, cardiovascular disease, diabetes, gout, fatty liver disease, some malignancies, elements of metabolic syndrome, and hyperactivity may be linked to high sugar intake.[6]

Artificial sweeteners

Artificial sweeteners are substantially sweeter than table sugar, require lower amounts to achieve to achieve the same level of sweetness, and either do not significantly increase the energy content of meals and beverages or are not metabolised in the human body. These have a low glycemic response and offer the sweetness of sugar without calories.[7]Certain ideal conditions must be met by artificial sweeteners. They should be inexpensive to produce, give sweetness without an unpleasant aftertaste, have few or no calories, not be mutagenic or carcinogenic when cooked, and not be damaged by heat. A physical or chemical substance that modifies an organism's genetic material is called mutagenic, whereas a carcinogenic agent can cause cancer.[8]Saccharin, acesulfame potassium, aspartame, neotame, and sucralose are the five main types of artificial sweeteners.

Since the middle of the 20th century, research has been conducted to determine how consuming sugar affects human health. Nonetheless, there is ongoing discussion over the functions of sugar in neurological, cognitive, and physical health. Consuming too much sugar has been linked to metabolic diseases, diabetes, cancer, heart disease, depression and cognitive decline in addition to obesityand many other[9] as shown in Fig 1. The paper aims to give a general idea about role of different sweeteners and sugars on human metabolic health and chronic diseases.

Effect of sugar intake on human health

Sweeteners and sugars have some effects on human health and metabolism. The effects of some common types of sugar that we generally consume in our diet are given below-

Glucose

The pancreas secretes insulin in response to glucose consumption. The brain's increased insulin signals tell us to quit eating because we've had enough. After ingesting glucose, our bodies go through several processes, but one in particular that happens in the liver creates very low-density lipoproteins (VLDL), which are linked to cardiovascular disease. Nevertheless, the liver

Table 1. Artificial sweeteners have relative sweetness compared to sucrose, their caloric content, and common applications.

No.	Common name	Common applications
1.	Saccharin	It is 200 to 700 times sweeter than sucrose and contains 0 kcal/g. It is commonly used in soft drinks, tabletop sweeteners, jams, chewing gum, and baked goods.[7]
2.	Acesulfame K	This sweetener is 200 times sweeter than sucrose with 0 kcal/g. It is used in tabletop sweeteners, candies, chewing gum, and dairy products.[7]
3.	Aspartame	Aspartame is 180 to 200 times sweeter than sucrose, providing 4 kcal/g. It is found in soft drinks, yogurt, and pharmaceuticals.[7]
4.	Neotame	Significantly sweeter, neotame is 7000 to 13000 times sweeter than sucrose with 0 kcal/g. It is used in baked goods, soft drinks, chewing gum, jams, jellies, puddings, and fruit juices.[7]
5.	Sucralose	Sucralose is 600 times sweeter than sucrose, also containing 0 kcal/g. It is used in frozen desserts, fruit juices, chewing gum, and gelatins.[7]

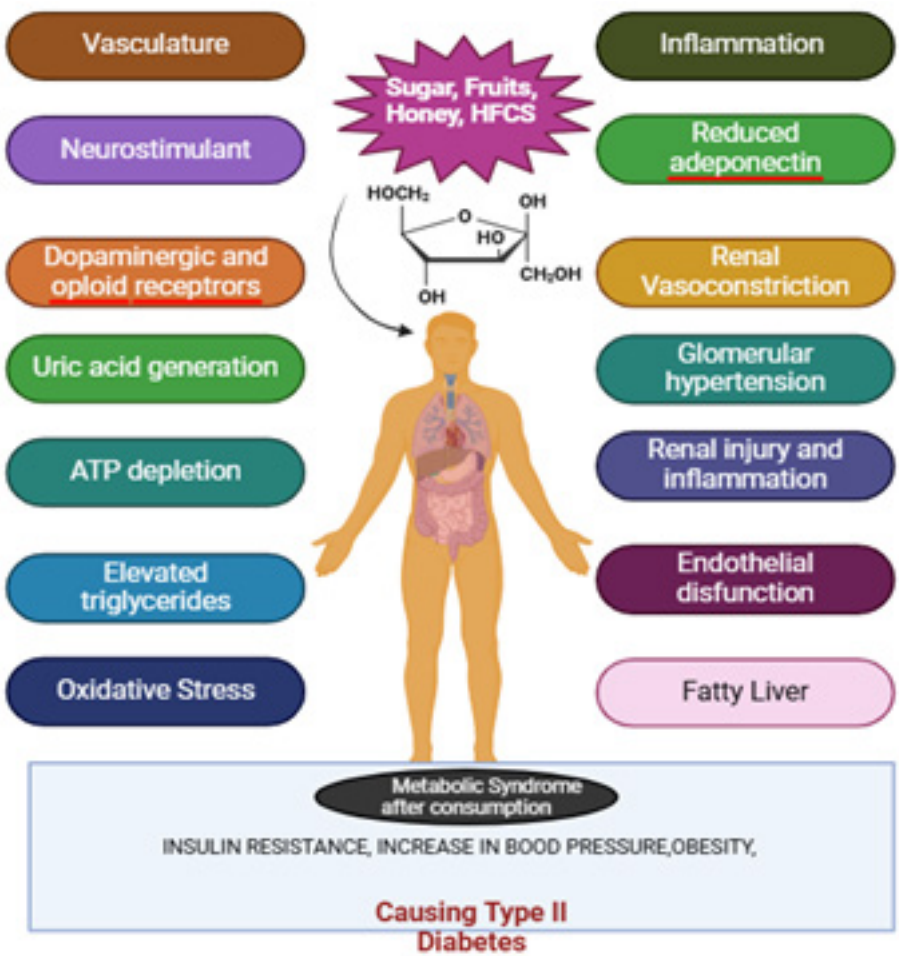

Fig. 1. Shows the effect of Sugar, honey, Fruits, and HFCS in different organs

processes glucose in our diet and turns it into VLDL in around 1 out of every 24 calories[10].

Sucrose and Fructose

Fructose is generally metabolized by the liver and along with fats large amount of VLDL is produced. The brain is unable to regulate the intake of fructose and sucrose carbohydrates because it is resistant to the protein leptin, which regulates energy intake and assesses the effectiveness of metabolism. This doesn't imply that consuming these carbohydrates will always be detrimental. When athletes consume these sugars, their livers become more filled with glycogen, which is then used for exercise and other athletic activities.[11]This attests to the fact that the consumption of sucrose and fructose is advantageous for people who engage in more physical activity and need quick energy.[10]

Glucosamine

This glyconutrient aids in preserving the health of the joints. It is a precursor to cartilage and aids in the management of osteoarthritis issues.[12]Glucosamine, a key component of glycosaminoglycans found in cartilage, has been studied for its potential therapeutic effects in osteoarthritis treatment.[13] Research indicates that glucosamine is preferentially incorporated into the galactosamine moieties of chondroitin sulfates in articular cartilage, facilitating proteoglycan production.[14]

Galactose

The sugar in milk is made up of glucose and lactose, a disaccharide. This sugar can also be found in a range of fruits, vegetables, and plants. Galactose facilitates calcium absorption, promotes quick healing from wounds, and enhances memory. [15]

Fucose

Fucose can only be found in significant quantities in the breast milk of humans, marine kelp, brewer's yeast, and certain types of mushrooms. Monosaccharide L-fucose is present in N and O-linked glycans and glycolipids that are made by mammalian cells. These play key roles in ontogenic events, host-microbe interaction, leukocyte-endothelium adhesion mediated by selection, and blood transfusion. Pathological diseases like as cancer and artherosclerosis are linked to change in their expression.[16] Consuming this sugar promotes long-term memory, guards against tumour growth and stops respiratory infections. Furthermore, they function as potent immune system modulators. Rheumatoid arthritis is linked to a lack of this sugar. Low levels of fucose are seen in patients with conditions such as diabetes, hepatic diseases and cystic fibrosis. Fucose plays a crucial role in the body's extrusion of the herpes virus. When applied, this sugar thickens and hydrate the skin, which also helps to minimise wrinkles.[10]

Table 2. An overview of various artificial sweeteners, their known metabolites, and their associated health risks, both acute and chronic

No.	Common name	Metabolites and its health risk
1.	Saccharin	Metabolized into O-sulfamoyl benzoic acid and is associated with acute symptoms like nausea, diarrhea, and vomiting. Chronic exposure can lead to serious conditions such as bladder cancer, low birth weight, and hepatotoxicity.[24,25]
2.	Acesulfame-K	Breaks down into acetoacetamide, which may cause headaches in the short term and has been linked to thyroid tumors over prolonged use.[26,27]
3.	Aspartame	Composed of methanol, aspartic acid, and phenylalanine. It may cause dizziness, nausea, vomiting, headaches, and thrombocytopenia acutely, with long-term exposure potentially leading to lymphomas.[7]
4.	Neotame	Metabolizes into methanol and de-esterified neotame. It can cause headaches and is hepatotoxic at high doses, with chronic exposure potentially resulting in weight loss and lower birth rates.[7]
5.	Sucralose	Noted for causing stomach pain, dizziness, and diarrhea, with chronic exposure leading to thymus shrinkage.[28]

Table 3. Effect of different kinds of free and added sugars on chronic diseases in humans

No.	Sugar responsible for the disease	Associated chronic diseases	Ref.
1	Fruit juice	High risk of diabetes mellitus	29
2	Sugar-sweetened beverages	Stroke risk increases	30
3	Sucrose	Sucrose is not related to diabetes mellitus	31
4	Sugar-sweetened beverages	Chronic heart diseases, increase inflammatory markers, increase triglycerides content	32
5	Soft drinks	Increase metabolic syndrome prevalence	33
6	Sugar- sweetened beverages	Diabetes mellitus	34
7	Soft drinks	Ischaemic stroke risk in men and women	35
8	Sugar-sweetened beverages	Increase metabolic syndrome risk	36
9	Sugar-sweetened beverages	Increase chronic heart disease incidence	37
10	Sugar-sweetened beverages	Low high density lipoproteins and increase rate of triglycerides	38
11	Added sugar	High stroke risk and decrease aortic stenosis	39
12	Sweet-sugar beverages	Increase cerebral infraction	40
13	Fructose	Increase rate of low density lipoproteins, increase rate of leptin and triglycerides	41
14	Fructose	Increase insulin, increase hepatic insulin resistance, increase body weight	42
15	Glucose and fructose	Increase visceral adipose tissue, increase liver fat, increase skeleton muscle fat, increase total cholesterol content	43
16	Fructose and glucose	Diabetes mellitus	44
17	Soft drinks or sweetened milk drinks	Diabetes mellitus	45
18	Sweet- sugar beverages	Cardio vascular diseases	46
19	Sweet-sugar beverages	High risk of diabetes mellitus in women	47
20	Sweet-sugar beverages	Increase liver fat	48
21	Sweet-sugar beverages	Increase metabolic syndrome risk in women, increase obesity prevalence.	49
22	Fructose	Increase postprandial de novo lipogenesis, increase rate of fasting glucose, increase fasting insulin, decrease insulin sensitivity index	50
23	Glucose	Increase body fat and weight, decrease fasting glucose.	50
24	Added sugars	Decrease high density lipoproteins, increase fasting insulin in overweight individuals only, increase insulin resistance in overweight individuals only	51
25	Added sugars	Increase cardio vascular disease mortality risk	52
26	Sweet sugar beverages	Increase inflammatory biomarkers, increase insulin, decrease adiponectin	53

Galactosamine

They can be found in some members of red algae Phaeophyceae, shark cartilage and crab shells. It facilitates communication between cells. Giving these sugars aids in controlling inflammation and the immunological system. It also essential for maintaining the health of joints. Cardiovascular disease is linked to its low levels.[10]

Mannose

An essential part of our immune system is mannose. Recent research suggests that mannose, a hexose sugar, may have unique anti-inflammatory properties compared to other dietary sugars. While excessive intake of glucose and fructose has been linked to increased inflammation and various non-communicable diseases.[17]It enters the bloodstream right away after absorption. Aloe vera is the primary source of it, but it can also be found in sea kelp, beans, capsicum, cabbage, tomatoes, and some mushrooms.[18]

Neuraminic acid

Colestrum, a special type of sugar, is

the first nourishment a mammal receives from its mother after parturition. The sugar is an essential component of the gangliosides found in the brain's grey matter. It is also present in the follicle-stimulatinghormone , which is necessary for ovulation.[19]

Xylitol and Erythritol

In light of the growing global usage of added sugars, xylitol and erythritol have gained significant popularity, particularly among individuals with diabetes. Natural sources of both sugars include fruits and veggies like lettuce, strawberries, raspberries, and plums.[20]Xylitol is a five-carbon alcohol sugar that is a perfect substitute for sucrose for diabetics because it has a lower glycemic index (13 against 65) and calorie content (2.4 versus 4.0 kcal/gram).[21] On the other hand erythritol is a four-carbon polyol ring is 60-80% sweeter than sucrose.[22] These two sweeteners' different metabolisms play a major role in determining how they affect metabolic diseases. For example, xylitol becomes partially absorbed in the upper gastrointestinal tract, it is then converted to D-xylulose by oxidation in the liver. This final product can now proceed through the pentose phosphate pathway, where the bulk of it will eventually be converted to glucose or a smaller amount of lactate.[20] Like artificial sweeteners, erythritol is quickly absorbed but not broken down, therefore it will eventually pass through the urine unaltered.[22]These sugar substitutes are considering the substitutes above, xylitol is thought to be safe for diabetics and quickly absorbed and excreted, preventing accumulation in tissues.[23]

Artificial sweeteners

Although artificial sweeteners don't raise blood sugar levels as they are not carbohydrates, they cause some other issues in human health, which are listed in table no 2.The effect of different kinds of free and added sugars on chronic diseases in humans is mentioned in Table no-3

CONCLUSION

The impact of sugars and artificial sweeteners on human metabolic health and chronic diseases is a critical area of research, especially given the alarming rise in diet-related health issues globally. This paper highlights the significant risks associated with excessive sugar intake, including obesity, diabetes, and cardiovascular diseases, while also acknowledging the potential adverse effects of artificial sweeteners. The findings underscore the need for a more comprehensive understanding of how these dietary components contribute to chronic diseases, emphasizing the importance of balanced consumption. In today's world, where processed foods and beverages are increasingly dominant in diets, understanding the long-term effects of sugars and sweeteners is more crucial than ever. Public health strategies must prioritize reducing added sugars and promoting the use of safer alternatives, potentially natural sweeteners with proven health benefits. Future research should focus on elucidating the mechanisms by which sugars and sweeteners influence metabolic processes, exploring their impact across diverse populations, and developing dietary guidelines that reflect these insights.The importance of this topic cannot be overstated, as it directly relates to global health challenges such as the obesity epidemic, the rising prevalence of diabetes, and the burden of cardiovascular diseases. Addressing the role of sugars and sweeteners in these conditions is essential for improving public health outcomes and reducing the incidence of diet-related chronic diseases. By fostering a deeper understanding and encouraging healthier dietary practices, we can make significant strides in promoting overall well-being and preventing the development of serious health conditions.

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This research did not involve human participants, animal subjects, or any material that requires ethical approval.

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This study did not involve human participants, and therefore, informed consent was not required.

Author Contributions

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REFERENCES

1. Priya K, Gupta DVRM, Srikanth K. Natural sweeteners: A complete review. Journal of Pharmacy Research. 2011;4(7):2034-2039.
2. Cummings J, Stephen A. Carbohydrate terminology and classification. European Journal of Clinical Nutrition. 2007;61(Suppl 1)
3. Walesh J, Cunningham S. The role of added sugars in pediatric obesity. Pediatric Clinics of North America. 2011;58(6):1455-1466.
4. Lustig R, Schmidt L, Brindis C. Public health: The toxic truth about sugar. Nature. 2012;482(7383):27-29.
5. Duffey K, Popkin B. High-fructose corn syrup: Is this what's for dinner? American Journal of Clinical Nutrition. 2008;88(6):1722S-1732S.
6. Burt B, Pai S. Sugar consumption and caries risk: A systematic review. Journal of Dental Education. 2001;65(10):1017-1023.
7. Whitehouse CR, Boullata J, McCauley LA. The potential toxicity of artificial sweeteners. Workplace Health & Safety. 2008;56(6):251-259. https://doi.org/10.3928/08910162-20080601-02
8. Zeynep F, Sifa T. Determination of the effects of some artificial sweeteners on human peripheral lymphocytes using the comet assay. Journal of Toxicology and Environmental Health Sciences. 2014;6(8):147-153. https://doi.org/10.5897/jtehs2014.0313
9. Beecher K, Cooper IA, Wang J, Walters SB, Chehrehasa F, Bartlett SE, Belmer A. Long-term overconsumption of sugar starting at adolescence produces persistent hyperactivity and neurocognitive deficits in adulthood. Frontiers in Neuroscience. 2021;15. https://doi.org/10.3389/fnins.2021.670430
10. Misra V, Shrivastava AK, Shukla SP, Ansari MI. Effect of sugar intake towards human health. Saudi Journal of Medicine. 2016;1(2):4-8. https://doi.org/10.21276/sjm.2016.1.2.2
11. Murray B, Rosenbloom C. Fundamentals of glycogen metabolism for coaches and athletes. Nutrition Reviews. 2018;76(4):243-259.
12. Matreja PS, Singh VK. Review study on effect of sugar over human health. Academicia: An International Multidisciplinary Research Journal. 2021;11(11):471-476.
13. Neil KM, Caron JP, Orth MW. The role of glucosamine and chondroitin sulfate in treatment for and prevention of osteoarthritis in animals. Journal of the American Veterinary Medical Association. 2005;226(7):1079-1088. https://doi.org/10.2460/javma.2005.226.1079
14. Noyszewski E, Wroblewski K, Dodge GR, Kudchodkar S, Beers J, Sarma A, Reddy R. Preferential incorporation of glucosamine into the galactosamine moieties of chondroitin sulfates in articular cartilage explants. Arthritis and Rheumatism. 2001;44(5):1089-1095.
15. Wolfe D. Essential Sugars: The Healing Power of Polysaccharides. 2011;5.
16. Becker DJ, Lowe JB. Fucose: Biosynthesis and biological function in mammals. Glycobiology. 2003;13(7):41R-53R. https://doi.org/10.1093/glycob/cwg054
17. Ma X, Nan F, Liang H, Shu P, Fan X, Song X, Hou Y, Zhang D. Excessive intake of sugar: An accomplice of inflammation. Frontiers in foology. 2022;13. https://doi.org/10.3389/fimmu.2022.988481
18. Rodríguez ER, Martín JD, Romero CD. Aloe vera as a Functional Ingredient in Foods. Critical Reviews in Food Science and Nutrition. 2010;50(4):305-326. https://doi.org/10.1080/10408390802544454
19. Barker S. Carbohydrates and the chemical industry: Achievements and prospects. Endeavour. 1991;15(4):155-157. https://doi.org/10.1016/0160-9327(91)90120-z
20. Schmid RD, Hovda LR. Acute hepatic failure in a dog after xylitol ingestion. Journal of Medical Toxicology. 2015;12(2):201-205. https://doi.org/10.1007/s13181-015-0531-7
21. Chukwuma CI, Islam MS. Effects of xylitol on carbohydrate digesting enzymes activity, intestinal glucose absorption and muscle glucose uptake: A multi-mode study. Food & Function.

2015;6(3):955-962. https://doi.org/10.1039/c4fo00994k
22. Boesten DMPHJ, Berger A, De Cock P, Dong H, Hammock BD, Hartog GJM, Bast A. Multi-targeted mechanisms underlying the endothelial protective effects of the diabetic-safe sweetener erythritol. PLoS ONE. 2013;8(6) https://doi.org/10.1371/journal.pone.0065741
23. Peterson ME. Xylitol. Topics in Companion Animal Medicine. 2013;28(1):18-20. https://doi.org/10.1053/j.tcam.2013.03.008
24. Reuber MD. Carcinogenicity of saccharin. Environmental Health Perspectives. 1978;25:173-200. https://doi.org/10.1289/ehp.7825173
25. Mahmood AR, Al-Juboori SB. A review: Saccharin discovery, synthesis, and applications. Ibn AL-Haitham Journal for Pure and Applied Science. 2020;33(2):43. https://doi.org/10.30526/33.2.2442
26. Xu X. The review: Effects of acesulfame K on human health. International Journal of Agriculture and Food Sciences Research. 2024.
27. Helal EG, Abdelaziz MA, Taha NM, El-Gama MS. The influence of acesulfame-k and aspartame on some physiological parameters in male albino rats. The Egyptian Journal of Hospital Medicine. 2019;75(1):1976-1981.
28. Silva MM, Reboredo FH, Lidon FC. Sweetener food additives: A synoptical overview on their chemical properties, applications in food products and side effects. Emirates Journal of Food and Agriculture. 2023;35(12):1-16.
29. Bazzano LA, Li TY, Joshipura KJ, Hu FB. Intake of fruit, vegetables, and fruit juices and risk of diabetes in women. Diabetes Care. 2008;31:1311-1317.
30. Bernstein AM, de Koning L, Flint AJ, Rexrode KM, Willett WC. Soda consumption and the risk of stroke in men and women. American Journal of Clinical Nutrition. 2012;95:1190-1199.
31. Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Diet and risk of clinical diabetes in women. American Journal of Clinical Nutrition. 1992;55:1018-1023.
32. de Koning L, Malik VS, Kellogg MD, Rimm EB, Willett WC, Hu FB. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. Circulation. 2012;125:1735-1741.
33. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D'Agostino RB, Gaziano JM, Vasan RS. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. Circulation. 2007;116:480-488.
34. Drouin-Chartier JP, Zheng Y, Li Y, Malik V, Pan A, Bhupathiraju SN, Tobias DK, Manson JE, Willett WC, Hu FB. Changes in consumption of sugary beverages and artificially sweetened beverages and subsequent risk of type 2 diabetes: Results from three large prospective U.S. cohorts of women and men. Diabetes Care. 2019;42:2181-2189.
35. Eshak ES, Iso H, Kokubo Y, Saito I, Yamagishi K, Inoue M, Tsugane S. Soft drink intake in relation to incident ischemic heart disease, stroke, and stroke subtypes in Japanese men and women: The Japan Public Health Centre–based study cohort I. American Journal of Clinical Nutrition. 2012;96:1390-1397.
36. Ferreira-Pêgo C, Babio N, Bes-Rastrollo M, Corella D, Estruch R, Ros E, Fitó M, Serra-Majem L, Arós F, Fiol M, Santos-Lozano JM, Muñoz MA, Razquin C, Sorli JV, Gómez-Gracia E, Martínez-González MA, Salas-Salvadó J. Frequent consumption of sugar- and artificially sweetened beverages and natural and bottled fruit juices is associated with an increased risk of metabolic syndrome in a Mediterranean population at high cardiovascular disease risk. Journal of Nutrition. 2016;146:1528-1536.
37. Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. American Journal of Clinical Nutrition. 2009;89:1037–1042.
38. Haslam DE, Peloso GM, Herman MA, Dupuis J, Lichtenstein AH, Smith CE, et al. Beverage consumption and longitudinal changes in lipoprotein concentrations and incident dyslipidemia in US adults: The Framingham Heart Study. Journal of the American Heart Association. 2020;9
39. Janzi S, Ramne S, González-Padilla E, Johnson L, Sonestedt E. Associations between added sugar intake and risk of four different cardiovascular diseases in a Swedish population-based prospective cohort study. Frontiers in Nutrition. 2020;7:603653.
40. Larsson SC, Akesson A, Wolk A. Sweetened beverage consumption is associated with lower risk of stroke in women and men. Journal of Nutrition. 2014;144:856–860.
41. Lê KA, Faeh D, Stettler R, Ith M, Kreis R, Vermathen P, et al. A 4-week high-fructose diet alters lipid metabolism without affecting insulin sensitivity or ectopic lipids in healthy humans. American Journal of Clinical Nutrition. 2006;84(6):1374–1379.
42. Lowndes J, Sinnett SS, Rippe JM. No effect of added sugar consumed at median American intake level on glucose tolerance or insulin

resistance. Nutrients. 2015;7(11):8830–8845.
43. Maersk M, Belza A, Stødkilde-Jørgensen H, Ringgaard S, Chabanova E, Thomsen H, et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: A 6-month randomized intervention study. American Journal of Clinical Nutrition. 2012;95(2):283–289.
44. Montonen J, Järvinen R, Knekt P, Heliövaara M, Reunanen A. Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. Journal of Nutrition. 2007;137(6):1447–1454.
45. O'Connor L, Imamura F, Lentjes MA, Khaw KT, Wareham NJ, Forouhi NG. Prospective associations and population impact of sweet beverage intake and type 2 diabetes, and effects of substitutions with alternative beverages. Diabetologia. 2015;58(7):1474–1483.
46. Pacheco LS, Lacey JV Jr, Martinez ME, Lemus H, Araneta MRG, Sears DD, et al. Sugar-sweetened beverage intake and cardiovascular disease risk in the California Teachers Study. Journal of the American Heart Association. 2020;9(4)
47. Papier K, D'Este C, Bain C, Banwell C, Seubsman S, Sleigh A, et al. Consumption of sugar-sweetened beverages and type 2 diabetes incidence in Thai adults: Results from an 8-year prospective study. Nutritional Diabetes. 2017;7(1)
48. Park WY, Yiannakou I, Petersen JM, Hoffmann U, Ma J, Long MT. Sugar-sweetened beverage, diet soda, and nonalcoholic fatty liver disease over 6 years: The Framingham Heart Study. Clinical Gastroenterology and Hepatology. 2022;20(11):2524–2532.e2.
49. Shin S, Kim SA, Ha J, Lim K. Sugar-sweetened beverage consumption in relation to obesity and metabolic syndrome among Korean adults: A cross-sectional study from the 2012–2016 Korean National Health and Nutrition Examination Survey (KNHANES). Nutrients. 2018;10(10):1467.
50. Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. Journal of Clinical Investigation. 2009;119(5):1322–1334.
51. Welsh JA, Sharma A, Cunningham SA, Vos MB. Consumption of added sugars and indicators of cardiovascular disease risk among U.S. adolescents. Circulation. 2011;123(3):249–257.
52. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among U.S. adults. JAMA Internal Medicine. 2014;174(4):516–524.
53. Yu Z, Ley SH, Sun Q, Hu FB, Malik VS. Cross-sectional association between sugar-sweetened beverage intake and cardiometabolic biomarkers in U.S. women. British Journal of Nutrition. 2018;119(5):570–580.