Effects of Sugar-sweetened (SSBs) and Artificially Sweetened Beverages (ASBs) in Cardiovascular Events: A Narrative review

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Abstract – *High fructose corn syrup (HFCS) has been widely used as sweetener for SSBs because of its economical and efficient qualities; however, it was linked to early onset of cardiovascular diseases (CVDs). One of the most important approaches to limit sugar intake is the substitution of artificial sugar in diet bottled beverages or also knowns as ASBs. Despite of the global acceptance on the use of artificial sweeteners in ASBs, different investigations postulated that chronic consumption of these products take a substantial role in the development of CVD. Thus, this review paper intends to provide synthesis of the literature on the effect of SSBs and ASBs on cardiovascular risks. An online search from different electronic databases such as PubMed, MEDLINE, BMJ Open Access and Science Direct was used to retrieve original articles which were published from January 2010 to August 2019. Extraction of data includes the title, authors, duration, characteristics of the sample used, exposure and outcome variables, limitations, and result of the study. Eleven (11) original articles were included in this study, six (6) SSBs and five (5) ASBs. Based on the reviewed articles, SSBs particularly those which use HFCS have direct link to CVD risks because of the metabolic pathway of fructose. Main rate-limiting steps of glycolysis is bypassed by fructose which can result to its efficient released to the circulation for extrahepatic metabolism or converted to fat or liver glycogen. The increase hepatic uptake of fructose can result to a large degradation of uric acid, adenosine triphosphate, and adenosine monophosphate which can amplify the CVD risks. Meanwhile, research studies have also shown that consumption of ASBs can also increase the risk of developing CVDs by alteration of gut microbiota. Related mechanisms involved in the development of CVD and its risk factors with consumption of SSBs and ASBs are gut dysbiosis resulting from altered gut microbiota and the neurobiological changes like increase in hunger sensation thus leading to higher food intake and body weight. Taken collectively, both SSBs and ASBs consumption are linked with the development and progression of CVD and its risk factors primarily caused by the biochemical alterations in carbohydrate metabolism leading to higher weight gain, blood sugar and atherogenic lipid levels. The consumption of any artificially sweetened beverages daily remains not a healthy option for the whole population. Intake of sweetened beverages including both with added natural and artificial sweeteners must be within the recommended levels.*

Keywords – *artificially sweetened beverages, cardiovascular outcomes, sugar-sweetened beverages*

INTRODUCTION

Metabolic effect of sugar has been a public health interest for decades because of its significant role in the development of negative health outcomes especially its role in the development of non-communicable diseases (NCDs) [1,2]. Use of fructose in the form of high fructose corn syrup (HFCS) has been widely used for sweetened products. However, scientific evidence shows that the use of HFCS was associated with NCDs. One of the best reasonable approaches to attain the sugar reduction in the diet is the use of non-caloric sweeteners or artificial sweeteners. Sweeteners in artificially sweetened beverages (ASBs) are potent stimulators of sweetness on the palate but containing little or no energy.

The use of artificial sweeteners was considered safe for consumption of human based on scientific studies that include the use of sucralose, acesulfame K, saccharin, neotame and aspartame [3]. Consequently, many food manufacturers use these sweeteners in food products particularly on beverages like sodas, bottled teas and all other which are expected to decrease the

negative consequences of consuming sugar-sweetened-beverages (SSBs) [4].

However, several studies suggested that intake of ASBs was linked with central adiposity, increased blood sugar levels which are risk factors for obesity and diabetes mellitus (DM). Consequently, obesity and DM are predominantly risk factors of cardiovascular disease (CVD). Obesity is highly correlated with insulin resistance and a state of pro-inflammation which marked a long-term increase in adrenergic activity, high blood sugar and dyslipidemia. The persistent metabolic stress due to pro-inflammatory effects result in continuous metabolic stress on the cardiovascular beds and subsequent chronic deterioration of myocardial structure which often leads to heart failure [5].

Regardless of the foregoing facts towards the consequences of high sugar intake particularly SSBs and ASBs, global consumption was continuously soaring across all age groups [6]. A growing trend in the consumption of SSBs has been also seen even among individual consuming Mediterranean diet, however it is still lower compared to global consumption [7].

OBJECTIVES OF THE STUDY

The increasing prevalence of non-communicable diseases particularly heart diseases call for methodological review of existing factor that might exacerbate CVD outcomes like consumption of SSBs. Furthermore, the introduction of different alternatives such as ASBs to reduce the negative outcomes of SSBs provides a paradox in many literatures. Thus, this review paper intends to provide synthesis of the literature on the effects of SSBs and ASBs on cardiovascular risks as well as provide biochemical explanations behind their effects.

MATERIALS AND METHODS

Research Design

This study utilized a narrative review through identification of eligible studies using different electronic databases such as PubMed, MEDLINE, BMJ Open Access and Science Direct for articles published from January 2010 to August 2019.This literature review used the following terminologies: *artificially sweetened beverages, sugar-sweetened beverages, cardiovascular diseases, consumption of artificially sweetened beverages, effect of artificially sweetened and sugar-sweetened beverages to cardiovascular health, and short- and chronic effects of artificially- and sugar-sweetened beverages to cardiovascular health.* Additional materials were recognized by manual identification of reference lists of reviewed articles.

Study selection

For the inclusion criteria, publications must be: (i) published in a reputable and peer-reviewed journals written in English language; (ii) studies using animal and human model were both considered; (iii) prospective and experimental studies were considered to be the major article for this review; (iv) the main objective of the paper is to examine the effects of artificially- and sugar-sweetened beverages towards the progression of CVD; and (v) the study used a valid research and statistical design to answer the research objectives. Based on the inclusion criteria, eleven (11) original articles were included in this study (SSBs=6) and (ASBs=5) after the selection of article for review.

Data extraction

The articles were recognized based on their abstracts and titles. Journals were retrieved and were included if the inclusion criteria are met. Extraction of data includes the title, authors, duration, characteristics of the sample used, exposure and outcome variables, limitations, and result of the study.

RESULTS AND DISCUSSION

Table 1 presents the articles used in this study to present the data on observational and experimental studies on the effect of SSBs on cardiovascular outcomes while Table 2 presents the studies focusing on the effect of ASBs on cardiovascular outcomes.

Observational studies suggest that consumption of SSBs primarily sweetened by fructose amplify the cardiovascular risk through alteration of the lipid levels including increased low-density lipoprotein cholesterol (LDL-chol), triglycerides (TG), and decreased high-density lipoprotein cholesterol (HDL-chol) levels [12,13]. Moreover, overweight women had a 140% increase in TG after consuming fructose-sweetened beverages for 10 weeks. This was supported by an animal experiment which concluded that plasma apoB concentrations and LDL-chol were also increased in the experimental animals that consumed fructose-SSBs but not for glucose-sweetened beverages [13].

Table 1. Observational and experimental studies on the effect of SSBs on Cardiovascular Outcomes

[Author/s] [Participants]	Results	Type of Study/Limitations
Fung TT et al., 2019 [8] n = 88,520 from Nurses' Health Study aged 34–59 years old	❖ After adjusting the confounding effect of dietary factors, the risk of developing CHD increases according to the cumulative average frequency of SSB consumption. The risk increases of developing CHD as consumption of SSBs increases. ❖ Consumption of >2 servings of SSBs per day among women increases the risk of developing CHD by 1.39 compared to those consumed less than one or never in a month.	❖ Cohort study design ❖ Recall bias ❖ Confounding variables which are not controlled in the statistical treatment.
Welsh JA, Sharma A, Abramson JL et al., 2010 [9] n=6113 adults from the National Health and Nutrition Examination Survey (NHANES) 1999-2006.	❖ The odds of having low HDL-chol level were most likely 50% to >300% higher among frequent SSBs drinker compared to the reference group (>5% and >10% added sugars). ❖ Adjusted mean HDL-chol levels were lower among participants that consumed higher level of added sugar to SSBs. The mean HDL-chol level tends to decrease and follow a linear trend as the level of added sugar increases from 58.7 mg/dl (5% energy from added sugar) and 47.7 mg/dl (17.5% to 25% energy from the added sugar.	❖ Cross-sectional study ❖ Recall Bias ❖ Misclassification bias ❖ Single dietary recall resulting to misclassification attributable of unmeasured variability
Stanhope KL and Havel PJ, 2008 [10] n=16 adult male rhesus monkeys (n=6 control; n=6 experimental)	❖ After 10 weeks, the one-day triacylglycerol and energy expenditure during the postprandial period tend to decrease among fructose-fed monkeys, whereas energy expenditure in glucose-fed monkeys remained unchanged. ❖ Effect of change in the body weight among monkeys that consumed glucose and fructose have been more likely related to the energy expenditure than in the energy intake.	❖ Experimental animal model
Khosravi-Boroujeni et al., 2012 [11] n=1,752 (782men/970 women)	❖ The odds of having higher energy intake of energy including all the food groups were associated with higher level of SSBs consumption.	❖ Cross-sectional design ❖ Misclassification bias ❖ Unadjusted risk estimates
Maersk M, Belza A, S.Jørgensen H, Ringgaard S, 2012 [12] Overweight subjects (n = 47) were randomly assigned to 4 different test drinks (1 L/d for 6 mo)	❖ Relatively higher result was observed between the baseline and end line results in the regular cola group compared to their counterparts. Higher level was found in total cholesterol, blood triglycerides, visceral fat, skeletal muscle fat, and hepatic fat. ❖ Mean changes were also significantly different in systolic and diastolic blood pressure between other beverage groups, higher mean was observed in the cola group. ❖ End line TG level was higher compared to the baseline among the cola group. ❖ Serum uric acid levels increased by 0.18 mg/dL among adolescents in the highest consumption of SSBs compared with lower intake when smoking, alcohol, intake of milk, diet beverage, and dietary fiber were controlled.	❖ Experimental design ❖ Small number of participants which limited the power of our statistical analyses. ❖ Non-blinding of participants
Jin R, Welsh JA, Le NA et al., 2014 [13]	❖ After 1-month intervention of providing glucose-sweetened beverage to reduce fructose intake from HFCS, considerable improvement in plasma free fatty acids was observed when compared to baseline. ❖ After 1-month intervention, change in the Very Low-Density Lipoprotein (VLDL) from baseline was significant between the reduced intakes of HFCS.	❖ Diet is not controlled in the study subjects over the intervention period. ❖ Replacement of dietary intake has been induced.
Nguyen S, Choi HK, Lustig RH and Hsu CY, 2009 [14] n=4867 adolescents aged 12 to 18 years	❖ Higher intake of SSBs were observed to increase the serum uric acid level by 0.50 mg/dL among participants compared to their counterpart with low SSBs intake. Meanwhile, after adjustment the effect of smoking, alcohol intake, fiber, and diet beverage intake the increase in serum uric acid was found at 0.18 mg/dl compared to participants with low SSBs intake.	❖ Misclassification bias ❖ Recall bias

Table 2. Observational and experimental studies on the effect of Artificial Sweetened Beverages (ASBs) on Cardiovascular Outcomes

Author/s	Results	Type of Study/Limitations
Pase MP et al., 2017 [15] 2888 participants aged >45 years for incident stroke	❖ Higher consumption of ASBs was linked with an increased risk of stroke. ❖ Association between ASBs and incident all-stroke was potentially mediated with hypertension (HPN).	❖ Observational study design ❖ Recall bias ❖ Misclassification bias
Gardner H et al., 2012 [16] n=2564 (36% men, 20% white, 23% black, 53% Hispanic)	❖ Regular intake of ASBs increased the risk of vascular events and the result is still significant after controlling the effect of metabolic syndrome, diabetes, elevated cholesterol levels, peripheral vascular disease, cardiac disease, and HPN. ❖ Levels of glycosylated hemoglobin (HbA1C) were significantly higher among the artificial sweetener group.	❖ Limited sensitive analyses
Suez J et al., 2014 [17] n=11 (glucose-fed) n=12 (saccharin-fed)	❖ At week 11, three groups (water, glucose, and sucrose) showed a similar curves of glucose tolerance, whereas the artificial sugar group also developed glucose intolerance.	❖ Animal model ❖ Used of saccharin, sucralose, or aspartame
Nettleton JA, 2009 [18]	❖ Any metabolic syndrome component at baseline of the extreme diet soda consumption categories had greater Hazard Risk (HR). ❖ After adjusting the effect of waist circumference and body weight, the effect remained significant across increasing diet soda consumption categories when compared with non-consumption.	❖ Use of Food Frequency Questionnaire ❖ Misclassification bias ❖ Recall bias
Mossavar-Rahmani R et al., 2019 [19] n=676 postmenopausal women (50 to 79 yo)	❖ Consumption of ASBs increases the risk for fatal and nonfatal stroke, ischemic stroke, CHD, all-cause mortality.	❖ Observational studies ❖ ASB consumption was self-reported

In relation to this, coronary heart disease (CHD) risk was associated with SSB-carbonated non-cola type beverages. After adjustments of non-dietary CHD factors, it was observed that there was a significant association between consumption of SSB and CHD risk. Particularly, intake of greater than 2 servings of SSB daily can increase the risk by 1.39 [8].

Meanwhile, higher intake of ASBs was associated with higher risk of ischemic stroke mediated by HPN. Observational studies also suggest that daily intake of ASBs elevated the risk of myocardial infarction (MI) similar with risks associated with intakes of SSBs [16,18].

Study of Nettleton et al. (2009) indicates that metabolic syndrome (MS) which is a predisposing factor of CVD was amplified by the increased consumption of ASBs. In a separate study, the risk of MS was increased by 36% higher among respondents who consumed ≥1 serving of diet soda daily [18]. Furthermore, an experimental study using animal model concluded that consumption of ASBs can also result in alteration of different biochemical parameters such as HbA1C which are indicators of glucose and insulin tolerance [17]. Moreover, in a recent study of Mossavar-Rahmani et al. (2019), it was found out that high level of ASBs intake significantly increased the likelihood to jeopardize all cardiometabolic endpoints and behavioral variables as well as increase the consumption of all other foods related to obesity [19].

Discussion

HFCS and Metabolism

The use of HFCS is very popular in the production of SSBs, fruit-flavored and carbonated beverages, and other baked products. Fructose metabolism is different from glucose in its major pathways. HFCS has an almost complete extraction through the presence of different enzymatic reactions during the first glycolytic fates of glucose and fructose [20].

The absorption of fructose in the gastro-intestinal tract to the portal vein will result to its efficient uptake in the liver resulting to production of fructose-1-phosphate in the presence of fructokinase. The resultant product will be divided eventually to two 3-carbon molecules: glyceraldehyde and dihydroxyacetone phosphate in the presence of aldolase. Glyceraldehyde-3-phosphate and dihydroxyacetone phosphate can go through in different metabolic pathways to create different substrates including fatty acids, lactate, glycogen, and glucose. These are not insulin-dependent processes; therefore, fructose can be metabolized without the secretion of insulin without increasing the blood sugar level [20].

Glucose metabolism is relatively different from the metabolism of fructose because of the almost full hepatic extraction and the different involvement of enzymes in the reaction during the initial metabolic steps. Fructose taken up by the liver are successively oxidized to carbon dioxide and eventually converted to lactate and glucose. These products are either released in the portal circulation which can be utilized for extrahepatic metabolism, converted to fat or liver glycogen. Efficient phosphorylation and fructose uptake in the liver can lead to degradation adenosine triphosphate to uric acid and adenosine monophosphate [20]. Compared to glucose, the main rate-limiting steps of glycolysis is bypassed by fructose in the presence of phosphofructokinase. Thus, resulting to de novo lipogenesis in the liver resulting to fat production.

SSBs and CVD Risk Factors of cardiovascular diseases

Alteration in blood lipids, increased level of uric acid and glucose level are all predisposing factors of cardiovascular diseases. Increased level of LDL and lower levels of HDL amplify the progression of atherogenesis process which eventually results to plaque formation. SSB consumption can substantially increases insulin concentrations and serum glucose [25]. Higher consumption of SSBs can significantly provide added glycemic load to the total diet of an individual. The increase in the glycemic load will lead to higher in the concentration of c-reactive proteins which may result to inflammation. This may result to thrombosis, atherosclerosis, and plaque stability which are all adverse CVD outcomes [26].

In a prospective study, it was observed that increased level of glycemic load increased the risk of developing CHD [27]. These effects could be facilitated by higher level of fructose in the diet. Furthermore, higher fructose intake was found to be a profound factor that can increase the de novo lipogenesis and synthesis of TG, and VLDL secretions in the liver that also reduces peripheral clearance of lipids [28,29]. Specifically, frequent consumption of fructose promotes lipogenesis in the liver through different pathways: fructose metabolism primarily happened in the liver; whereas it bypasses the main rate-limiting step of glycolysis via fructose-1-phosphate catalyzed by phosphofructokinase that provides uncontrolled level of fat substrates including Acetyl-CoA and glycerol-3-phosphate. Lastly, the sterol receptor is also independently regulated by insulin due to elevated fructose level [30].

Lastly, it was also observed that higher salt intake resulted to higher SSBs consumption also leads to higher intake of salt that may contribute to higher blood pressure [31]. Higher consumption of salt can activate the aldose reductase–fructokinase pathway in the hepatic cells and hypothalamus which can result to endogenous production of fructose resulting to leptin resistance and hyperphagia. This can eventually result to obesity, insulin resistance, and fatty liver. [32]

This can also result to decreased urinary excretion of sodium and higher level of serum uric acid which can potentially increase the systemic blood pressure [33]. It was also observed that children with primary HPN tend to have elevated level of serum uric acid compared to their healthy counterparts [34].

In a prospective cohort study conducted in US, it was found out that consumption of SSBs was associated with CVD risks. The risk was even increase when the frequency of consumption was increased; consumption of >2 servings of SSB daily had a higher compared to those who are consuming <1 serving per month of SSB. Holding other variables constant, it was also observed that there is also a positive association between cola-type beverages and CVD risks. The observed associations were similar for non-carbonated beverages such as punches and fruit drinks, however it is not statistically significant. Similar observations were observed for non-carbonated punches and fruit. These results were still significant even after women who were diagnosed with diabetes, angina, or coronary bypass surgery were excluded [8].

ASBs and CVD Risk factors

Positive correlations were found between artificial sugar consumption and some metabolic syndrome parameters [18] like the presence of

atherogenic lipid profile. Sweet sensation in the tongue and its activating genes is said to be involved in de novo lipogenesis of acetyl coA carboxylase and fatty acid synthase. One potential mechanism is that the TAG-rich lipoproteins mediated by the postprandial hypertriacyglycerolemia stimulates the remodeling of the atherogenic lipid profile [35].

In a study of consumption of aspartame as artificial sweetener, it was observed that it resulted in greater glucose intolerance in obese individuals. In this same study, it was also found out that respondents in the artificial sugar group had higher body mass index (BMI) and obese individual that consumed saccharin developed impaired glucose tolerance compared to their non-saccharin consumer counterparts [36]. Also, in the study of Suez et al. (2014), it was observed that saccharin consumption can result to glucose intolerance among lean individuals.[37]. Evidence from both rodent and human research suggests that saccharin may be associated with the early progression of CVD outcomes [38].

In relation to other studies, it was also observed that high intake of ASBs had considerably greater chance of developing CVD adverse outcomes except hemorrhagic stroke even after holding other variables constant. It was found out that the likelihood of developing CHD was 1.29 higher compared to non-consumers of ASBs [19].

Based on the reviewed studies, the link can be explained by possible alteration of the gut microbiota which results to gut dysbiosis [17] which progress on impaired insulin secretion and gastric emptying [39]. Meanwhile, supporting to this evidence was the role of artificial sugar in the changes in taste perception which is linked to increase in body weight [40,41] which can also impede the dysregulation of glucose homeostasis [42].

Increase in body weight was relate to changes in some biochemical parameters which are all associated in progression of cardiovascular diseases by increasing the risks through atherogenesis process [18,19]. Impaired insulin secretion would impede the development of DM which is also associated in the development of cardiovascular diseases focusing on its role in cardio myopathy [43]. DM seems provide a direct link to cardiomyopathy than exclusively through HPN and coronary atherosclerosis. The DM-cardiomyopathy has been described as changes that happen in left ventricular structure and cardiac functions [44,45].

Related Mechanisms Between SSBs & ASBs and Cardiovascular Risks

Different studies focused on the role of artificial sweeteners in neurobiological changes particularly on the appetite-regulatory system. In the study of Pereira (2013), consumer of ASBs tends to have higher BMI which are dependent in the amount of intake [46]. Postulated mechanism is that aspartame consumption can elevate the subjective hunger compared to natural sweeteners [47]. Compared to sucrose and glucose, artificial sugars can preload or increased the food intake [48]. Artificial sugars used in ASBs were all associated with increased food intake, wherein aspartame has the most significant effect since it does not have an aftertaste [49].

Another major link between the negative cardiovascular outcomes and artificial sugars can be described by the altering mechanism of artificial sweeteners to gut microbiota resulting to glucose intolerance and dysbiosis. It was observed that α-gustducin and sweet taste-receptors respond with artificial sweeteners (acesulfame-K and sucralose) similar with sucrose and glucose [50, 40]. These receptors serve as critical mediators of glucagon-like peptide-1 (GLP-1) secretion along with GLP-1 secreting L cells found in gut mucosa. Hence, a stimulation of intestinal taste receptors occurs with sucralose administration which in turn leads to increase absorption of sugar in the bloodstream from the intestine [50, 51]. In related studies, intake of ASBs before an oral glucose resulted to secretion of GLP-1 that eventually led to altered insulin secretion and gastric emptying [42, 42, 52]. Thus, the consumption of artificial sugars together with other foods or beverages rich in simple sugar may potentiate the absorption of sugar, secretion of insulin and GLP-1 which eventually lead to increased appetite, body weight and hyperglycemia [43, 50, 52].

Limitation of the study

This review article aimed to present and consolidate the evidences from various research studies the role of SSBs and ASBs consumption in the development of CVDs and its risk factors. This article has included studies of various designs involving both human and animal models. No limitations were set for variables including exposure, intervention, or outcome which may confound overall analysis and interpretations. Lastly, the discussions made were purely based on the included studies combined with

concepts of nutritional biochemistry particularly on carbohydrate metabolism.

CONCLUSION AND RECOMMENDATION

Taken collectively, both SSBs and ASBs consumption are linked with the development and progression of CVD and its risk factors primarily caused by the biochemical alterations in carbohydrate metabolism leading to higher weight gain, blood sugar and atherogenic lipid levels. The consumption of any artificially sweetened beverages daily remains not a healthy option for the whole population. Intake of sweetened beverages including both with added natural and artificial sweeteners must be within the recommended levels.

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