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NUTRITION AND AGING (Y GU, SECTION EDITOR)

Substitution of Sugar-Sweetened Beverages for Other Beverages: Can It Be the Next Step Towards Healthy Aging?

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Abstract

Purpose of Review With the prolongation of life expectancy, the gap between lifespan and "health span," the disease-free lifespan, has been widening due to the massive burden of age-related chronic diseases and research on healthy aging has been gaining momentum. A growing body of evidence suggests that diet is a strong determinant of healthy aging and consumption of sugar-sweetened beverages (SSB), a major source of added sugars, predicts poor health outcomes in the aging population, including cardiovascular disease, diabetes, and cancer. Evidence further supports a link between sugar-sweetened beverages-triggered pathological processes and biologic factors of aging, including inflammaging, oxidative stress, and alterations in intestinal microbiota. At present, substitution of sugar-sweetened beverages with healthier alternative beverage remains the most robust strategy to limit the deleterious effects of sugar-sweetened beverages on health worldwide and may help achieve healthy longevity. The purpose of this review is to provide an overview of mechanisms by which sugar-sweetened beverages consumption may impact the physiological aging process and how a simple intervention of beverage replacement may promote healthy aging.

Recent Findings Recent findings indicate that SSB are associated with accelerated aging phenotype and activate various adverse biological processes such as chronic inflammation, oxidative stress, insulin resistance, and gut dysbiosis.

Summary Replacing SSB with healthier beverages may be a reasonable option to reduce the burden of chronic disease in the aging population and even prolong life and healthspan.

Keywords Healthy aging · Sugar-sweetened beverage · Inflammaging · Oxidative stress · Intestinal microbiota · Chronic kidney disease

Introducing the Concept of Healthy Aging

With the extension of life expectancy, which is reaching 79 years in the USA [1], population demographics are changing immensely in developed nations. Thanks to the advances in our understanding of individual diseases processes, many people can survive with chronic diseases and reach old ages. However, the burdens of multiple comorbidities and disabilities of aging accumulate and decrease the quality of life as people live longer. The major morbidities in people aged 60 years and older include chronic kidney disease (CKD) and cardiovascular diseases (CVD) (30%), malignant neoplasms (15%), chronic respiratory diseases (10%), musculoskeletal diseases (8%), and neurological and mental disorders (7%) [2]. The raising concern for the well-being and functional independency with the increasing lifespan denotes the longevity phenomenon. The concept

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of "healthy aging" was introduced in response to the need to focus on "healthspan," the disease-free lifespan, rather than lifespan itself. Healthy aging encompasses both physical and cognitive functioning and is a life-long process that ideally starts in childhood and evolves around the goal of prevention [3•]. Evidence suggests that lifestyle interventions, including diet and physical activity, can help achieve healthy aging [4•]. Indeed, healthy dietary patterns have been found to be protective against many diseases including metabolic syndrome [5], type 2 diabetes (T2DM) [6], CVD [7], cancer [8], and Alzheimer's disease [9•] and to have a strong inverse correlation with overall mortality [10, 11]. Among particular food groups, consumption of sugars and artificially sweetened beverages deserves special attention due to their strong association with poor health outcomes. As a major source of fructose and glucose, sugar-sweetened beverages (SSB) may interfere with several components of healthy aging mainly by triggering inflammatory response and contributing to the development of chronic diseases. The aim of this review is to provide an overview of ways SSBs can impact the aging process and potential benefits of substituting alternative beverages for SSBs in promoting healthy aging.

Sugar-Sweetened Beverages, Artificially Sweetened Beverages, and Health

SSBs have been consumed extensively over the past decades and constitute as much as 20% of the daily total energy intake and 24% of the total added sugar intake in the USA [12, 13]. It is estimated that approximately one-half of the US adult population consume at least one serving of SSB per day [14]. Nevertheless, excess SSB intake has widely recognized health risks, including obesity, T2DM, CVD [15–18], CKD [19], and depression [20]. Strikingly, analysis of the NHS and HPFS cohorts for 34 years revealed a dose-graded association between SSB consumption and higher risk of total, CVD, and cancer mortalities [21•]. Additionally, SSBs may contain additional food additives that may adversely affect health. As an example, cola drinks may contain inorganic phosphate. Inorganic phosphate from food additives is fully absorbed in the gut, contrary to natural phosphate contained in foods [22]. Excess dietary phosphate may overwhelm kidney excretion capacity, especially if this is already compromised by inflammation- or kidney disease-driven Klotho deficiency [23]. Indeed, a positive phosphate balance is a key component of the accelerated aging phenotype of Klotho-deficient mice [23].

The detrimental effects of SSBs are accepted to be mainly mediated by its high fructose content. In contrast to glucose, fructose has an insulin-independent metabolism which bypasses the first rate-limiting glycolysis steps and induces glycogenesis, gluconeogenesis, and lipogenesis. As the majority of fructose is metabolized in the liver, excess ingestion promotes hepatic lipid accumulation [24, 25], ATP depletion [26], and oxidative stress, resulting in the development of nonalcoholic steatohepatitis [25–28]. Meanwhile, lipid dysregulation may contribute to the fructose-induced weight gain [29] and metabolic syndrome [30].

Studies of fructose-induced metabolic syndrome, a widely used experimental model of metabolic syndrome in rats, have identified various fructose-induced metabolic disturbances including hyperglycemia, hyperinsulinemia, and insulin resistance as well as hyperuricemia, hypertriglyceridemia, and hypercholesterolemia [31]. Cohort and experimental studies also corroborated that fructose intake has an important link with dyslipidemia [32], weight gain [33], fatty liver disease [34], and metabolic syndrome [35] in humans. Importantly, metabolization of high amounts of fructose induces oxidative stress via production of reactive oxygen species (ROS) and depletion of antioxidants [31]. Together with its contribution to systemic inflammatory activation and glycation processes that will be discussed later, fructose-induced oxidative stress mediates tissue and endothelial injury interlinked with the development of overt T2DM and its associated micro- and macro-vascular complications [36, 37].

In addition to the direct effects of the sugar load in SSBs, consumption of SSBs may urge other unhealthy dietary habits. Evidence from clinical trials suggests that SSB intake modulates neurobehavioral patterns that perpetuate consumption in a feed-forward manner and may reinforce the hedonic motivation towards the intake of other high sugar food [38•]. Higher SSB consumption has been consistently associated with poorer diet quality, higher daily caloric intake, and greater intake of discretionary foods [39]. Increased caloric intake and unhealthy diet further contribute to the development of obesity-related diseases and metabolic derangements.

Therefore, whether or not fructose is the main culprit, the evidence of SSB's long-term detrimental effects on health is unequivocal. SSB consumption is established to impede healthy aging by contributing to the burden of chronic diseases and may further be linked to functional impairment and frailty in the elderly population. Although there have been no studies investigating the direct relationship between SSB consumption and combined healthy aging indexes such as cognitive function; social well-being; and psychological well-being, added sugar appears to negatively affect various parameters such as frailty [40••], cardiovascular disease [41•], type 2 diabetes [42], hypertension [43], bone health [44], body composition [45], dental health [46], nonalcoholic fatty liver disease [47], inflammation [48•], and mortality [49•].

Data from a cohort of Spanish adults over 60 years old found that participants who consumed more added sugar were more likely to develop frailty, whereas no association was seen for sugars naturally present in foods [50••]. Insulin resistance and elevated serum C reactive protein (CRP) levels, which are favored by SSB consumption and will be discussed later, were also associated with incident frailty in adults aged 69 to 74 years in the analysis of the Cardiovascular Health Study [51].

The Role of Sugar and Sweetened Nutrients in Aging

SSBs potentially shorten lifespan as well as healthspan, while their role in the pathophysiology of aging remains to be explored. In this section, the possible mechanisms by which SSB consumption and sugar overload may contribute to the aging process (Fig. 1) will be discussed.

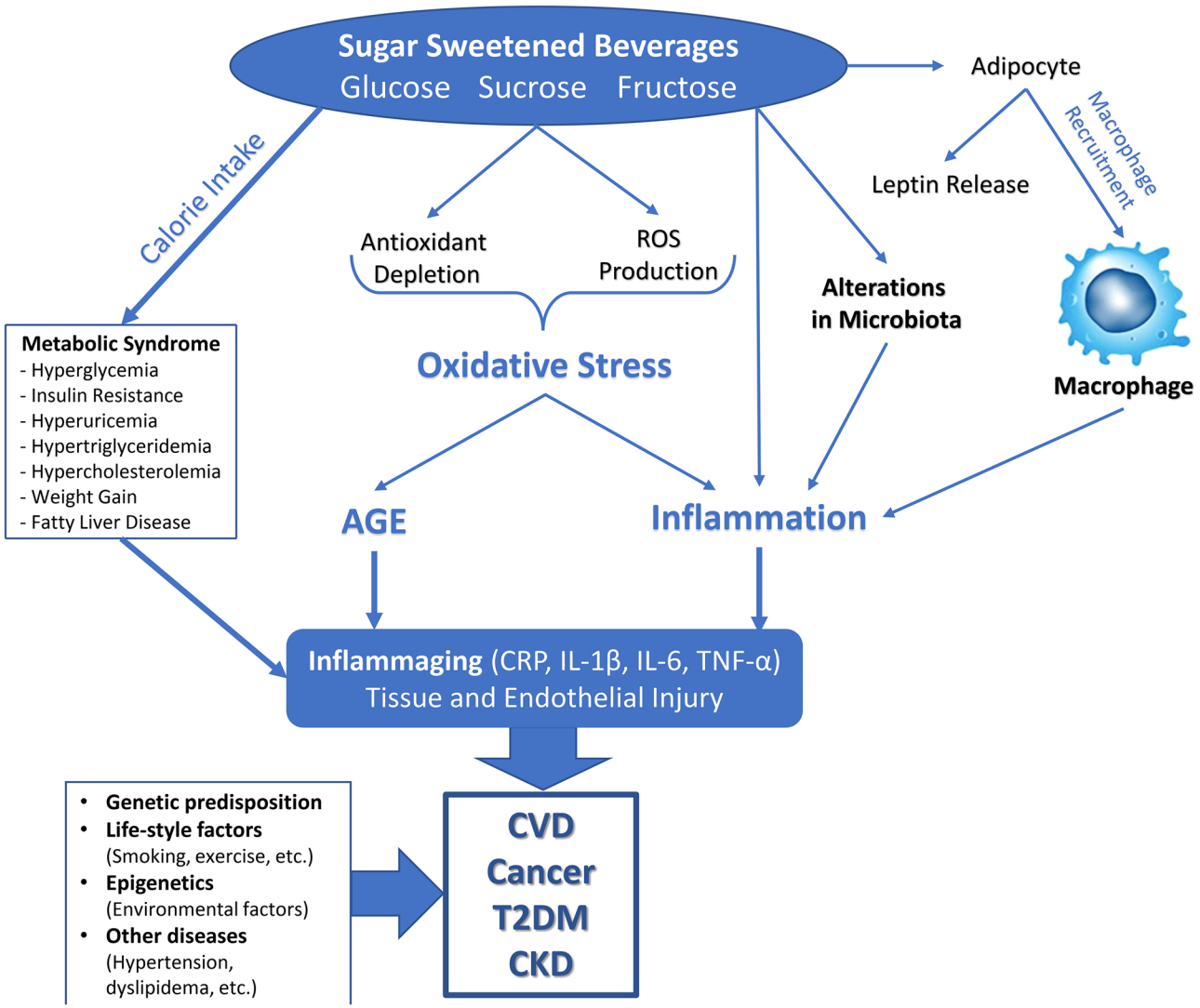

Fig. 1 Pathways to the detrimental effects of sugar-sweetened beverages (SSB). There are several mechanisms by which SSBs may incite the development of chronic diseases. Through their sugar load, which may primarily be glucose, sucrose, or fructose, SSBs increase daily caloric intake and lead to excess weight gain, the primary trigger for the development of metabolic syndrome. Fructose metabolism depletes cellular antioxidant stores and promotes the production of reactive oxygen species (ROS). The accumulation of oxidative damage leads to cellular senescence and aging and contributes to the pro-inflammatory state already directly induced by the sugar overload. The inflammatory activation caused by sugar metabolism, oxidative stress, alteration in the gut microbiota, and macrophage recruitment in adipose tissue accelerates the inflammaging process. Excess calorie-related metabolic derangements and inflammation incite endothelial and tissue injury, which are the bases of major age-related chronic diseases such as CVD, T2DM, cancer, and CKD. ROS, reactive oxygen species; CRP, C reactive protein; IL, interleukin; TNF, tumor necrosis factor

1-Inflammaging

One hallmark of the aging process is the progression of a low-grade, chronic inflammatory state called inflammaging. This sterile, subclinical, systemic inflammatory activation is now hypothesized to be a main driver of the increasing susceptibility to chronic disease and frailty with growing age [52••]. Most elderly people, even those without risk factors or clinically active disease, have high circulating levels of pro-inflammatory markers. Although there is no standardized measure of inflammaging yet, these high levels of cytokines, most commonly CRP, IL-6, and TNF-α, are used as the main indicators of inflammaging and strongly predict age-related morbidity [53••]. Specifically, inflammaging is an independent risk factor for CVD [54], CKD [55], cancer [56], and cognitive decline [57], as well as for functional decline and disability [53, 58, 59•]. However, questions remain on the origin of inflammaging and whether its relationship with age-related disease is one of causality. One of the hypothesized driving forces of inflammaging is visceral obesity (Fig. 2). In obese individuals, adipose tissue in the abdomen and liver is a prominent source of pro-inflammatory cytokines including IL-6 and TNF, due to the T cell and macrophage populations it harbors [60]. The chemokines released by migrating T and B lymphocytes induce adipocytes to produce adipokines that further aggravate the inflammatory milieu and increase the levels of pro-inflammatory markers in the circulation [53, 61]. Weight loss through calorie restriction results in down-expression of inflammation-related genes in adipocytes, accompanied by a substantial decrease of pro-inflammatory markers [62]. Indeed, weight loss also improved functional status and the risk of CVD in obese elderly individuals [63], although its association with attenuated inflammatory state is uncertain [53].

Consumption of SSBs may have a role in the process of inflammaging via several effects. Mounting evidence suggest that SSB consumption is associated with elevated inflammatory markers [64–68]. Given the strong association between increased adiposity and pro-inflammatory cytokine production, SSBs have been proposed to induce inflammatory factor production through its caloric content [48]. A robust body of evidence points to a key role of SSBs in weight gain and the pandemic of obesity [69–71]. Through aggravating visceral obesity, SSBs may an inflammatory milieu, and thereby inflammaging. SSB consumption has also been linked with increased markers of inflammation independently of body mass index (BMI) [67 68].

NHANES data disclosed that heavy SSB drinkers had a 0.26 mg/dl higher CRP concentration compared to non-SSB drinkers after adjustment for confounders including BMI, total energy intake and physical activity. However, further analysis revealed BMI to be an

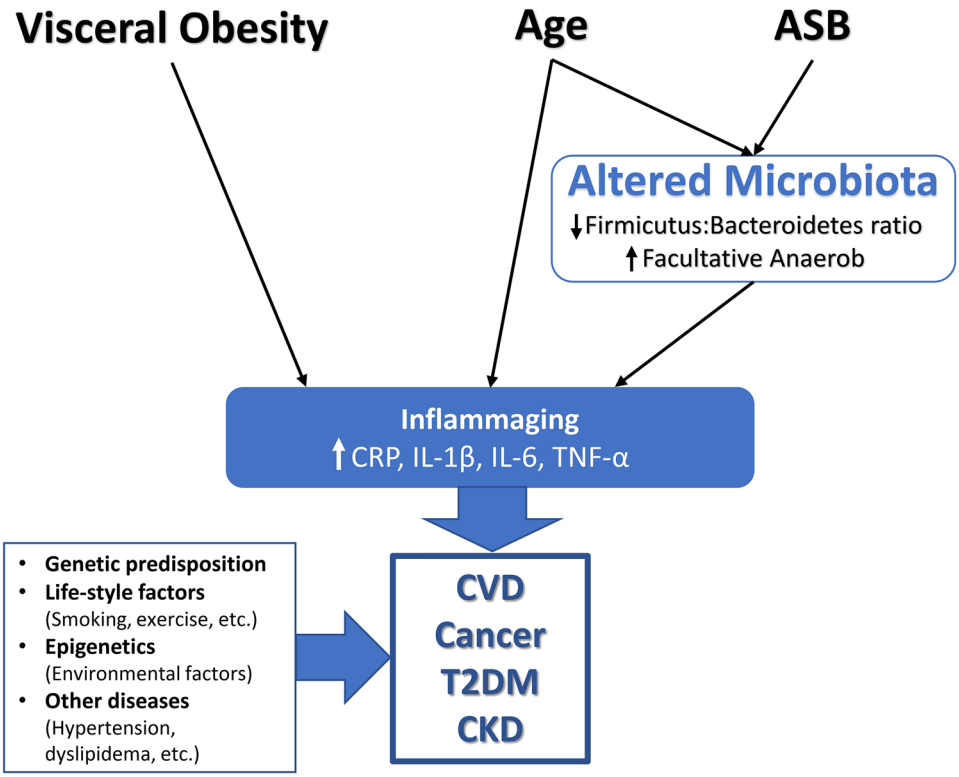

Fig. 2 Effects of visceral obesity, aging, and artificially sweetened beverages (ASB) consumption. Two key factors of aging pathophysiology are inflammaging and altered gut microbiota. Visceral obesity promotes inflammaging through the secretion of inflammatory factors and adipokines from visceral fat tissue. ASB consumption, on the other hand, has been shown to produce microbiota changes that mimic the microbiota changes seen in the elderly. The resulting inflammaging is a key risk factor for the development of age-related chronic diseases including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), cancer, and chronic kidney disease (CKD). CRP, C reactive protein; IL, interleukin; TNF, tumor necrosis factor

effect modifier; the association between SSB intake and CRP levels was significant only in obese participants. Recently, fructose, the main sugar in SSBs, has been suggested to provoke low-grade inflammation in adipocytes through macrophage recruitment and upregulated leptin release [72]. Thus, the high fat tissue mass in obesity could amplify the inflammatory effects of fructose to a level of clinical significance. Under such circumstances, the share of SSBs in the process of inflammaging would be expected to be more prominent in the obese elderly, whose diet may also be more inclined to include added sugars and SSBs. Still, fructose may not be the only sugar in the SSBs to blame. A randomized controlled crossover trial has reported that SSB intake increased CRP levels regardless of whether the SSB contained fructose, glucose, or sucrose [64]. Regardless of the exact mechanism, the relationship between SSBs and systemic inflammatory status should be regarded with caution in the elderly. Given that only 3-week intake of small to moderate amounts of SSB is enough to cause a significant rise in CRP levels [64], SSB consumption possibly puts extra inflammatory burden to the already ongoing inflammaging process in elderly.

2-Intestinal Microbiota

Another component of the complex relation between aging and diet is gut microbiota. Diet has a well-known relationship with gut microbiota, a key regulator of many biologic and immunologic processes. Regarding its complex interaction with chronic conditions like obesity and inflammatory diseases [73•], intestinal microbiota has been proposed to be a possible element of healthy aging [74]. Indeed, composition of gut microbiota is known to evolve through lifetime and to increase inter-individual variability with increasing age [73]. Aging microbiota has been characterized by an increasing abundance of subdominant species [74] and specifically a reduction in the Firmicutes:Bacteroidetes ratio along with over-representation of facultative anaerobes [75, 76]. Overall, aging microbiota has low biodiversity, which is associated with increased health risks [77••]. Existing literature also demonstrates a direct correlation between healthy microbiota and attenuated markers of inflammation, implying a possible key role of microbiota in inflammaging. Indeed, certain microbe compositions including over-representation of Proteobacteria and underpresentation of anti-inflammatory Faecalibacteria have been correlated with increased pro-inflammatory cytokine levels [76]. Short-chain fatty acids, such as butyrate or crotonate, are among the gut microbiota products known to dampen inflammation, either through epigenetic mechanisms related to post-translational histone modifications or to activation of specific receptors [78].

The effects of SSB's high fructose and glucose load on microbiota can negatively impact healthy aging via two main mechanisms: by aggravating the systemic inflammatory state of inflammaging and by upsetting the delicate balance of intestinal microbial species. High-fructose and high-glucose diets increase the abundance of pro-inflammatory Proteobacteria and the expression of inflammatory cytokines, such as TNF-α and IL-1β in mice [79]. Importantly, high fructose intake increases intestinal permeability, causing microbial translocation from the intestinal lumen to the portal circulation. The resulting endotoxemia instigates a low-grade systemic inflammatory state, as well as local liver inflammation which drives nonalcoholic fatty liver disease [80, 81]. Both high fructose intake and obesity rearrange the delicate microbiota composition. However, the exact "obese" microbiome is still equivocal and various publications provide contradicting results about the effect of high-fructose diet on the Firmicutes:Bacteroidetes ratio [82–84]. Notwithstanding the dispute, it is accepted that excess fructose and sugar substitutes alter microbiota composition and restrict diversity [84]. Although the impact of SSB on the aging microbiota has not been identified, better diet is directly associated with rich microbiota diversity in the elderly. Preservation of the diversity is of paramount importance in this population particularly due to its correlation with favorable health/frailty parameters [73].

3-Oxidative Stress and Glycation

Age-induced accumulation of oxidative damage has been one of the most explored hypotheses on the drivers of cellular aging, currently termed the Oxidative Stress Theory of Aging [85]. The theory postulates that over time, oxidatively damaged biomolecules (DNA, proteins and lipids) build up in cells and initiate cellular senescence. High ROS levels maintain cell senescence, exhaust the stem cell pool, and favor apoptosis over cellular repair [86••, 87]. ROS-induced switch into senescence-associated secretory phenotype (SASP) involves secretion of various chemokines and interleukins including IL-1, IL-6, and TNFα, via activation ofnuclear factor kappa-B (NFκB) along with secretion of degradative enzymes like matrix metalloproteases [88•]. The state of oxidative stress is further aggravated by the weakening of the antioxidant defense system during aging, characterized by decline in superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) activities [89]. These changes in the cellular environment constitute the biological bases of the age-related functional losses in organ systems and chronic pathological processes such as CVD, T2DM, neurodegenerative disorders, and cancer [86].

Glucose and fructose, or added sugars in general, are direct inducers of ROS and may modulate cellular aging through various oxidative pathways. Hyperglycemia

generates high levels of ROS via NADPH oxidase activation, mitochondrial glucose oxidation, and oxidative glycosylation [90]. Fructose is a more potent inducer of oxidative stress and glycation [91] pertaining to the differences in their metabolisms. The exhaustion of antioxidant defenses and release of ROS by fructose metabolism is a major factor linked to endothelial dysfunction and increased risk of CVD [92], the pathogenesis of T2DM [93], and fatty liver [28]. Regarding the deleterious effects of fructose on oxidative balance, the sugar content of SSBs appears to be connected with age-related functional decline in both cellular and systemic levels.

Added sugars are directly related to another well-recognized hallmark of aging, glycation, which occurs naturally with time as well as pathologically in many disease processes including diabetes and renal failure. Accumulation of advanced glycation end products (AGEs) and related cellular dysfunction induces age-related tissue damage [94]. The glycation reaction is greatly enhanced by hyperglycemia and oxidative stress, two pathologic conditions induced by added sugar, hence SSB, consumption [95]. In the light of this evidence, SSB consumption appears capable of accelerating "physiological age" via boosting the naturally occurring aging processes.

4-Caloric Restriction

Lastly, regardless of the sugar subtype they contain, SSBs are a major source of extra calories. The only known intervention to consistently maximize longevity and decrease biological rate of aging in a wide range of species from unicellular organisms to mammals is caloric restriction. Caloric restriction by 30% without malnutrition increases lifespan up to 50% in short-living species such as rodents [96]. The rhesus monkey genome shares a sequence identity of approximately 93% with human genome [97] and aging physiology is strikingly similar to humans [98]. In three independent studies of rhesus monkeys, caloric restriction effectively slowed aging and improved overall health and function [98–100], although results of its impact on lifespan are mixed [100]. In contrast to findings from Wisconsin National Primate Research Center (WNPRC) [98] and the preliminary data from The University of Maryland [99], National Institute on Aging (NIA) [100 documented no significant impact of caloric restriction on survival. Later, the authors from WNPRC and NIA together presented a direct comparison of the longitudinal data from both studies and attributed the discrepancies between the results to key differences in study designs and implementations. Consequently, the authors concluded that both studies confirm the health benefits of caloric restriction in monkeys through mechanisms likely translatable to humans [101].

Studies on nonhuman primates are of paramount importance, since a long-term clinical trial to assess the effects of a life-long caloric restriction on human lifespan and aging has not been conducted and does not seem feasible. Still, epidemiological and observational studies in centenarians suggest long-living humans share a very similar phenotype with adults following a calorie-restricted diet (including low body weight, short stature, and lean BMI) [102•, 103]. The Okinawans, the world's longest-lived people, are known for their traditionally low caloric diet starting from young ages andlife-long low BMI [104]. In addition to their extended average and maximum lifespans, the population living on Okinawa, an island in Japan, have low risk and delayed onset of chronic diseases, denoting an extended healthspan [104].

The first randomized trials of caloric restriction in healthy non-obese humans, the CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) trials, were initiated by the US National Institute of Aging in three clinical sites [105]. Caloric restriction induced significant weight loss, improved cardiometabolic risk factors, and significantly decreased markers of oxidative stress, inflammation, and DNA damage without a decrease in quality of life [105–107]. Two years of sustained caloric restriction showed metabolic adaptations similar to those thought to increase longevity in calorie-restricted rodents [107], fasting serum insulin and core body temperature which correlated with life expectancy inanimal studies [108]. Overall, the results are promising for greater benefits of caloric restriction-induced metabolic adaptation in the long term.

Yet, it should be underlined that the extend of the effects of caloric restriction appears to depend on the age of onset [101]. Archived dietary and anthropometric data estimate that the Okinawan population was in a negative energy balance of approximately 10% and Okinawan septuagenarians and centennials had been calorically restricted at least until middle age, resulting in a very lean adult population in caloric restriction phenotype [104]. Using data from rodent studies, it has been predicted that 20% caloric restriction from age 25 to 72 would yield a 5-year life extension, while 30% caloric restriction from age 55 to 72 would yield only a 2-month gain [108].

While the long-term effects of caloric restriction on aging in humans have not been confirmed, the detrimental effects of excess caloric intake and resulting weight gain on health span and longevity are clear. Obesity has well-recognized links with major morbidities including T2DM, CVD, and cancer as well as with all-cause mortality [109]. BMI over the normal range is associated with higher risk of premature death in healthy people at baseline [109]. In the NHS cohort, being overweight or obese was the strongest risk factor for premature death, with a population attributable risk of 22% [110]. In our

current obesogenic environment, SSB intake makes a substantial contribution to the consistent positive energy balance. In some reports, routine SSB consumption has been associated with an increase in daily total calorie intake of 226 kcal [39]. In fact, consumption of SSBs seems to increase the net positive energy balance more than consumption of solid food with equal sugar content since sugars induce little satiety when ingested in a beverage [111]. Hence, consumption of caloric beverages significantly during meals does not reduce solid food intake and consequently increases the energy intake [112]. Interestingly, such effect seems to be independent of the type of sugar used in SSBs. In a randomized crossover trial, consuming 4 servings of SSB per day for 8 days significantly increased ad libitum energy intake, regardless of the fructose and glucose content of the beverage. While there was no difference between the effects of fructose, glucose, or high-fructose corn syrup-sweetened beverages, artificially sweetened beverages (ASB) did not cause a change in total energy intake [113]. Verifying these findings, consumption of SSBs has been recognized as a determinant of body weight among people consuming ad libitum diets in a systemic review commissioned by the World Health Organization. SSB-induced increase in body fatness was mediated by the increase in energy intake rather than the sugar content, as isoenergetic exchange of sugars with other carbohydrates did not induce weight change [114]. Reducing SSB consumption, on the other hand, is an effective intervention to accomplish weight loss or avoid excess weight gain [115, 116]. Last but not least, SSBs are not only sources of increased caloric intake. Increased fat intake and ultra-processed foods are also important causes of increased caloric intake. As deleterious daily habits are associated with combined adverse eating patterns (both increased SSBs, fat, processed food, and carbohydrate intake), the independent effect of increased SSBs intake on increased caloric intake is hard to measure precisely. Thus, not only decreasing SSBs intake but also fat, processed food and carbohydrate intake should be targeted to reduce increased caloric intake

Substituting Healthy Alternative Beverages

From a public health standpoint, the need to limit SSB consumption is indisputable. The recommended alternatives include beverages with low calories, especially plain water, artificially sweetened beverages (ASBs), coffee, and tea as well as beverages with higher nutritional value such as milk and 100% fruit juice [117] (Table 1). Of these, 100% fruit juice is a source of carbohydrates deprived of most of the fiber contained in fresh fruit. In this regard, fresh fruit has a high water contents (e.g., 86% in oranges) and should be preferred. Additionally, ASBs frequently contain additional additives that per se may have a negative impact on the gut microbiota and health, as, for example, inorganic phosphates.

Evidence suggests that substitution of SSBs by alternatives is associated with long-term health benefits in addition to lowering calorie intake and helping weight loss. The analysis of NHS II cohort data estimated that substitutions of SSBs and fruit juices by plain water, ASBs, milk, coffee, or tea for more than 20 years were all significantly

Table 1 Comparison of the health implications of sugar-sweetened beverages (SSB), artificially sweetened beverages (ASB), and alternative beverages

	SSB	ASB	Alternatives (water, tea, coffee, milk)
Content	Glucose, fructose, sucrose [64]	Saccharin [126]	-
Calorie intake	High [36]	Lower calorie	Ranging from zero to lower calorie
Weight change	Weight gain [69–71]	Weight gain [71]	Weight loss [82]
Risk of metabolic syndrome	Yes [30]	Yes [58]	None
Effect on microbiota	Altered microbiota composition [84]: -Increase pro-inflammatory Proteobacteria [64] -Restricts diversity [84]	Decrease in Firmicutes:Bacteroidetes ratio [126]	-
Risk factor for	Obesity [15–18] T2DM [15–18] CVD [15–18] CKD [15–18] Depression [19] Cancer [21]	Hypertension [127] T2DM [128, 129] CVD [130] Stroke [131, 132] Dementia [89]	Decreased risk of T2DM especially with coffee or milk [75]
Mortality	Increase [21]	Increase [21]	Protective [10, 11]

T2DM type 2 diabetes mellitus, *CVD* cardiovascular disease, *CKD* chronic kidney disease

associated with decreased risk of T2DM [118]. Notably, substitution of coffee or milk for SSBs resulted in the highest risk reduction (12–17%) [118], a previously shown phenomenon [119] possibly owing to the polyphenol content [120]. Similarly, estimate analysis of the NHS I, NHS II, and HPFS cohort data together noted that replacement of one daily serving of SSB with water, coffee, or tea, but not ASB, was associated with a 2–10% lower diabetes risk in 4 years [42].

Among healthy replacements, a strong emphasis is placed on the consumption of drinking water, which is an optimal beverage alternative owing to its easy accessibility. Dietary Guidelines for Americans advocate drinking water as the primary beverage [13] and water has been recommended to comprise at least 20% of fluid requirements [121]. Due to its zero caloric content, replacing SSBs with drinking water is an exceptionally effective strategy to lower total energy intake [122]. In a randomized controlled trial with 240 overweight/obese participants, nutritional counseling targeted on substituting water for SSB resulted in more than 20-kg weight loss on average by the end of 9 months. Notably, the intervention decreased the prevalence of metabolic syndrome among obese but not overweight participants [123]. A greater response in the obese participants, a population with greater risk, provides yet another evidence on the role of baseline BMI as an effect modifier.

Nevertheless, the CHOICE trial showed that replacement of SSBs with water or ASBs induced an average weight loss of 2 to 2.5% over 6 months in overweight and obese adults. While no significant difference was seen in weight losses between the groups, the water-consuming group had a significant reduction in fasting glucose compared to the ASB-consuming group [116].

Using the NHANES dataset, a nationally representative data from US adults, and previously reported weight changes in randomized controlled trials, Duffey et al. modeled the impact of replacing SSB with water on obesity prevalence in the adult population. The study predicted that replacement of one serving of SSB with water would significantly decrease the prevalence of obesity from 35.2 to a predicted of 33.5% and increase the prevalence of normal BMI from 29.7 to a predicted of 31.3% [124].

The global trend in increasing ASB consumption deserves special attention in this discussion. Beverages with noncaloric artificial sweeteners have been used worldwide as a "healthy" alternative to SSBs. Owing to their low caloric content, ASBs have been considered beneficial and increasingly recommended for people suffering from obesity, metabolic syndrome, and T2DM [125]. Ironically, mounting evidence link ASB consumption with weight gain and metabolic syndrome [71]. Through compositional and functional alterations to the intestinal microbiota, ASB may induce glucose intolerance [126]. It is noteworthy that in animal studies, saccharin, a major component of ASBs, was also found to decrease the Firmicutes:Bacteroidetes ratio and lead to associated metabolic derangements that were similar to the changes in the aging microbiota (Fig. 2) [126].

Indeed, large cohort studies indicate long-term associations between ASB consumption and health outcomes. ASBs have been associated with higher risk of hypertension [127], T2DM [128•, 129], CVD [130], stroke [131••, 132], and dementia [131••]. Notably, the analysis of two large US cohorts confirming the dose-graded association of SSBs with mortality also showed a significant association between long-term high consumption of ASBs and mortality [21]. Nevertheless, it is still unclear whether the associations of ASBs with health outcomes are confounded by reverse causation, as people with higher risk may prefer ASBs over SSBs later in life. While the long-term benefits and possible harms of ASBs are debated, one reason of their ongoing popularity is the belief that replacing SSBs with ASBs would be easier in large scales owing to the sweet preference in general population. However, recent publications suggest substituting water for SSBs instead of ASBs may be just as successful. Online implementation intentions to substitute SSB intake with either water or a diet drink was found to be equally effective in reducing SSB intake within 2 months [133]. Nevertheless, ASBs may have the additional benefit of satisfying the hedonic liking for sugar and consequently decreasing added sugar intake from solid food according to the NHANES data. When compared with higher water intake, higher ASB intake was found to correlate with lower consumption of carbohydrates and sugars, lower hemoglobin A1c (HbA1c) levels, and lower risk of insulin resistance [134]. Until further investigations determine the most efficacious beverage alternative to replace SSB, American Heart Association recommends the use of alternative beverages other than ASBs with a focus on water [135]. In the meantime, there is sufficient data to conclude that substituting SSBs with alternatives is a successful strategy to promote health and prevent SSB-associated disease risk in the aging population

Future Perspective

A major goal in the future of healthcare is translating the increase in lifespan into an equal increase in healthspan. SSB consumption contributes to the development of many age-related chronic diseases, especially T2DM, and therefore shorten healthspan. Furthermore, findings of limited studies imply a possible negative impact of SSBs on frailty. There is sufficient compelling evidence that substituting SSBs for healthier options may decrease the burden of chronic disease in the aging population and even prolong life and healthspan.

Some health policies to decrease SSB consumption are already being developed. These include the application of an excise tax on SSBs [136], front-of-package health warning [137], and vending machine restrictions [120]. Public endorsement of consumption of healthier beverage alternatives should include health campaigns and public education to change the social norms on beverage consumption in every socioeconomic level.

Lastly, given that several essential processes of aging, including inflammaging, oxidative stress, and alterations of gut microbiota, may potentially be modulated by SSB consumption, future studies should address whether substitution of SSBs with healthier beverages may delay the rate of biological aging.

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Drafted the work or revised it critically for important intellectual content: Baris Afsar, Adrian Covic, Alberto, Ortiz, Mehmet Kanbay. Approved the final version to be published: Lale A. Ertuglu, Adrian Covic, Abdullah B. Yildiz, Baris Afsar, Alberto Ortiz, Mehmet Kanbay

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