Chronic High Fructose Intake in Beverages and SARS-CoV-2

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Fructose intake from SSBs increased during the COVID-19 lockdown. Chronic high intake of fructose activates several damage-associated processes of lung injury, including renin-angiotensin system (RAS) activation, uric acid (UA) levels, aldose reductase (AR) activity, and advanced glycation end products (AGEs) production. These molecular mechanisms are involved in lung injury induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

fructose | sugar-sweetened beverages | lung diseases | COVID-19

1. Introduction

Fructose is a monosaccharide present in fruits, vegetables, and honey, and is a constituent of the disaccharide, sucrose. In modern diets, however, the main source of fructose monosaccharide is high-fructose corn syrup (HFCS), which is used as a sweetener in various foods, mostly sugar-sweetened beverages (SSBs). SSBs are any non-alcoholic water-based beverages with added sugar, including sodas, fruit drinks, sports/energy drinks, pre-sweetened iced tea, and artificially sweetened homemade beverages. Since the 1970s, fructose intake has increased to 7.5% of total energy intake (equivalent to 37.5 g of fructose), due to the substitution of sucrose for HFCS in SSBs [1]. Epidemiological studies have reported that SSBs consumption is high in several countries globally, and often in large amounts, contributing to the overall energy density of diets [2]. A survey of 187 countries found that SSBs consumption in adults is higher in middle-income countries than in high- or low-income countries [3]. In high-income countries such as Australia, the United Kingdom, the United States, and Canada, the consumption of SSBs was 0.55, 0.50, 0.66, and 0.51 servings/day, respectively [3]. In the middle-income countries in the Caribbean and Latin America (LATAM), the highest consumption of SSBs was observed worldwide, with an average consumption of 1.93 and 1.61 servings/day, respectively, compared to 0.58 servings/day globally [4]. In particular, Mexico presented an average SSBs consumption of 1.21 servings/day [3], which represented 17.5% (325 kcal; equivalent to 81.25 g of sugar) and 19.0% (382 kcal; equivalent to 95.5 g of sugar) of total daily energy intake per capita in children aged 1 to 19 years and adults aged ≥20 years, respectively [5]. This increase in fructose consumption through SSBs has caused the rise of non-communicable diseases (NCDs), including obesity, non-alcoholic fatty liver disease, cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), some cancer types, and lung diseases [6]. The Caribbean and LATAM have the highest mortality from NCDs related to SSB consumption worldwide, with around 159 deaths per million adults (compared to 48 deaths per million adults

globally) [7]. However, the understanding on the relationship between chronic high intake of fructose and lung damage in common lung diseases is still generating new evidences.

2. Chronic High Intake of Fructose and Its Potential Involvement with COVID-19 Severity

Leading health agencies have suggested that a healthy diet improves immune system function, which could reduce risk factors for coronavirus disease 2019 (COVID-19) [8][9]. The WHO recommends limiting the consumption of added sugar to less than 10% of the total energy intake for the proper functioning of the immune system [10][11]. However, fructose consumption from SSBs increased during the COVID-19 lockdown. A cross-sectional study of 3916 US participants reported that 21.6% of adults drank more SSBs, while 9.6% drank often or always during the COVID-19 lockdown [12]. An observational study enrolling 1000 Spaniards with a mean age of 51 years reported that consumption of SSBs had increased in participants who gained weight during the COVID-19 lockdown, compared with those who did not gain weight (71.0% vs. 23.1%, $p < 0.001$) [13]; however, a COVID-19 health survey of 28,029 Belgian participants aged ≥ 18 years showed that consumption of SSBs increased both in participants who gained weight (9.2%) and in those who did not (8.7%) during the COVID-19 lockdown [14]. Data, obtained from Peruvian participants in the Perusano (pre-COVID-19) and the Stamina (COVID-19) surveys, showed a high prevalence of SSBs consumption in both populations (>78.0%) [15].

Fructose consumption from SSBs has been associated with hospitalization and mortality from COVID-19. A case-control study of 93 active-duty US Air Force members hospitalized for COVID-19 (median age of 26 years, and BMI of 25.9) found that those who consumed 3 to 6 servings/week of SSBs were more likely to be hospitalized (OR = 1.34; 95% CI: 0.61–2.92), while those who consumed ≥4 servings/day were even more likely to be hospitalized (OR = 5.23; 95% CI: 0.67–40.9) [16]. An ecological study including 158 countries found that the crude mortality rate of COVID-19 was raised with increasing consumption of SSBs (Beta: 0.340; $p < 0.001$); interestingly, it decreased by increasing fruit consumption (Beta: −0.226; $p = 0.047$), and beans and legumes (Beta: −0.176; $p = 0.046$) [17]. This indicates that high fructose consumption may exacerbate the disease severity, although molecular mechanisms associated with fructose-induced lung injury in COVID-19 patients are unknown.

There are clues about the molecular mechanisms that could be involved in the lung injury induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which may be deregulated by fructose. For example, ACE2, a component of the RAS, acts as the target receptor for SARS-CoV-2, allowing virus entry and replication in host cells, including alveolar epithelial cells [18]. SARS-CoV-2 can downregulate ACE2, and the loss of pulmonary ACE2 activity is associated with acute lung injury [19]. A study including 893 COVID-19 patients reported that those chronically receiving ACE inhibitors and Ang II receptor blockers (ARB) had a lower risk of admission to the intensive care unit (OR: 0.49; 95% CI: 0.32–0.73), and death (OR: 0.23; 95% CI: 0.14–0.38), compared to those receiving no treatment [20]. In another study, COVID-19 patients receiving RAS inhibitors (hazard regression (HR) = 0.499, 95% CI: 0.325–0.767) or ARB (HR = 0.410, 95% CI: 0.240–0.700) showed a lower risk of all-cause mortality [21]. In the case of UA, a retrospective study of 1149 COVID-19 patients found that UA levels were elevated in patients who ultimately died (>400 µmol/L), compared to recovered patients (≤400 µmol/L) (OR: 3.17, 95% CI:

2.13–4.70; $p < 0.001$). UA levels were positively correlated with inflammatory markers such as ferritin, TNF-α, and IL-6 [22]. Another study reported that elevated serum levels of UA (≥423 μm/L) were associated with an increased risk of intensive care unit admission (OR: 1.8; 95% CI: 0.83–3.98), mechanical ventilation requirement (OR: 2.41; 95% CI: 1.06–5.46), and death (OR: 3.01; 95% CI: 1.16–7.81) [23]. Regarding AR activity, an open-label clinical trial with 10 COVID-19 patients found that treatment with AT-001 (AR inhibitor) was associated with reduced hospital stay and reduced mortality [24]. Moreover, in a case of SARS-CoV-2 infection in a 57-year-old male, it was reported that the patient recovered after the use of AT-001 drug [25]. For the RAGE, an observational cohort study reported that COVID-19 patients had high sRAGE levels in correlation with SOFA score [r_s (162) = −0.525, $p < 0.001$] [26]. sRAGE levels were higher in patients who ultimately died [U(Ndeath = 11, Nsurvival = 153) = 1520.50, z = 4.46, $p < 0.001$] [26]. A cross-sectional study of 145 COVID-19 patients showed elevated serum sRAGE levels in patients with severe disease (1.47 [0.97–2.25] ng/mL) compared to those with non-severe COVID-19 (0.78 [0.63–1.00] ng/mL); an association between serum sRAGE levels and COVID-19 severity was found ($r = 0.598$; $p < 0.001$) [27]. Finally, a study in 23 asymptomatic COVID-19 patients and 35 COVID-19 patients with lung involvement found that the asymptomatic patients had elevated sRAGE levels (17.5 ng/mL) compared to patients with lung involvement (2.05 ng/mL) [28].

3. Conclusion

The COVID-19 pandemic high-fructose intake has shown many roles in respiratory diseases [29] and has been associated with hospitalization and mortality from COVID-19. Evidence suggests that several molecular mechanisms involved to lung injury induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may be deregulated by high fructose intake, resulting in worsening of symptoms. Therefore, it is needed more studies for elucidated the relationship of fructose consumption and lung injury.

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