COMMENTARY

High fructose corn syrup (HFCS) plays a dominant role in the pathogenesis of NAFLD-associated cirrhosis

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OBJECTIVE: The use of high fructose corn syrup in the food and beverage industry has shown an increase in the past few decades. Our aims were to evaluate the role of HFCS in inducing nonalcoholic fatty liver disease (NAFLD) and following conditions such as nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis.

METHODS: In this study, we browsed through the PubMed database by entering the keywords "non-alcoholic fatty liver disease", "fructose", "fibrosis" and "cirrhosis". We also included Basaranoglu's previous extensive research studies on fructose, NAFLD and NASH.

RESULTS: The adverse effects of high fructose corn syrup (HFCS) in cirrhosis formation were demonstrated in animal studies. When mice were fed with excessive trans fat, they developed NASH, however cirrhosis formation was not observed. When the mice were fed a combination of trans fat and HFCS, cirrhosis formation was completed.

CONCLUSION: The increased consumption of fructose from food and beverages and the rising rates of obesity have shown a parallel increase. The prevalence of NAFLD, a condition that is associated with obesity, hyperlipidemia and insulin resistance has also shown a similar increase, which may progress to more severe forms such as cirrhosis. In conclusion, we have identified the excessive consumption of fructose in the form of HFCS as a key contributor to the development of cirrhosis.

Key Words: *Fructose; Corn syrup; Pathogenesis; NAFLD; Cirrhosis*

Fructose is a simple polysaccharide that naturally occurs in fruits and vegetables. Before the advancements in the food industry, fructose was limited in the human diet, which people mostly obtained from honey, raisins, dates, figs and molasses.

The combination of fructose and glucose, forming the disaccharide sucrose, has been used as a dietary component since the Middle Ages, during times when it was rather a luxury preserved for the royalty. Sucrose or table sugar, was derived from sugar cane in the Indian subcontinent and sent to Europe for consumption. With the increase in cane planting and sugar export, sugar became a more common dietary component available to the public. In the 1970s, fructose entered the food and beverage industry in the form of high-fructose corn syrup (HFCS) as an alternative to sucrose. Longer shelf life and lower cost were two benefits brought by the introduction of HFCS a sweetener. Such benefits helped increase the popularity of fructose as an ingredient.

METHODS

In our bibliographic database search, we have looked at studies which have demonstrated a positive correlation between obesity and NAFLD or advanced liver disease, as well as between the increasing rates of fructose consumption and NAFLD with fibrosis. The increasing rates of fructose consumption which grow in parallel with the increase in obesity and overweight were shown in several studies, also supported by nation-wide health survey results. The data collected by National Health And Nutrition Examination Survey (NHANES) indicate that fructose consumption in children and adults in the United States has increased from 37 g/day (8% of daily total caloric intake) in 1977-1978 to 54.7 g/day (10.2% of daily total caloric intake) (1).

The increased consumption of fructose has become a major risk factor for the development of not only obesity, but also fatty liver disease, argue Basaranoglu et al. (2). In their research study, they aim to answer the question of whether there is a link between the increased consumption of fructose and increased prevalence of fatty liver disease. The excessive accumulation of triglycerides in hepatocytes in the absence of significant alcohol consumption is defined as non-alcoholic fatty liver disease (NAFLD) and may lead to inflammation of the liver - non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis or hepatocellular carcinoma (3). Understanding the underlying causes of NAFLD is essential to producing preventive and treatment strategies for this chronic liver disease, note Basaranoglu et al. (2). Obesity related cytokines such as interleukin-6, adiponectin, leptin and tumor necrosis factor-alpha are some of the factors that contribute to the development of NAFLD. Type 2 diabetes is another risk factor for NASH, with or without obesity. Dietary factors such as the type of diet consumed play a significant role in developing fatty liver disease and liver injury (4).

RESULTS AND DISCUSSION

Basaranoglu et al. (5) have shown the adverse effects of a high-fructose diet on metabolism in their previous research. A diet that is high in cholesterol, saturated fat and fructose is called a "cafeteria" or "fast food" type and it produces a gene expression signature of inflammation, increased hepatic fibrosis, endoplasmic reticulum stress and lipoapoptosis. A diet that is high in fat, on the other hand, leads to obesity, insulin resistance and hepatic steatosis with minimal inflammation, yet no fibrosis. By comparing the results obtained from two groups of mice, one group fed a high-fat diet and the other fast food diet containing fructose; they successfully showed that consumption of fructose in quantities relevant to that consumed by most Americans induced weight gain and metabolic abnormalities. In addition, it was shown that mice fed with excessive trans fat developed NASH, however cirrhosis formation was not observed. When the mice were fed a combination of trans fat and HFCS, cirrhosis formation was completed (5).

NAFLD-associated cirrhosis, fructose and obesity

Non-alcoholic fatty liver disease is a form of chronic liver disease that has the potential to progress to non-alcoholic steatohepatitis, cause the formation of fibrosis in the liver, and lead to more advanced diseases such as cirrhosis or hepatocellular carcinoma. Studies show that the prevalence of NAFLD show an increase parallel to body mass index (BMI). The prevalence of NASH as a precursor of NAFLD-associated cirrhosis is 3% and 20% in non-obese and obese subjects, respectively, according to a study by Basaranoglu et al. (6). In another study by Sinn et al. (7), it was found that the NAFLD prevalence that is 15% in non-obese patients increases in obese [BMI=30.0-39.9 kg/m^2] and extremely obese (BMI ≥ 40.0 kg/m^2) patients to 65% and 85%, respectively

In a large Swedish cohort study with a 39 years follow up period, where 44,248 male subjects were observed, the authors tested the association between BMI and a diagnosis of decompensated liver disease, cirrhosis, or liver-related death. It was seen that BMI and being overweight is a significant

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risk factor for developing severe liver disease, independent of other risk factors such as alcohol consumption (8).

In a study by Abdelmalek et al. (9) where 341 NAFLD patients were analyzed, it was found that daily fructose intake was associated with a higher stage of fibrosis. Also, in older adults, daily fructose consumption was found to be associated with increased hepatic inflammation and hepatocyte ballooning (9). The fibrosis promoting effects of fructose were also demonstrated in a recent study by Cydylo et al. (10), in which twenty-seven monkeys were fed diets either low or high in simple carbohydrates, in the form of fructose [control and high fructose diet], on low-fat, cholesterol-free background. The subjects consumed the high fructose diet for up to seven years and their liver tissue was analyzed for fat and fibrosis content. It was seen that consuming a high fructose diet induces hepatic steatosis and fibrosis (10).

One important point to consider is the form from which fructose is obtained. The fructose obtained from HFCS differs from the fructose that is naturally present in fruits and vegetables in the way that it lacks the essential nutrients and fiber that fruits and vegetables provide. Moreover, research show that due to its metabolism, a single load of fructose causes hepatic lipid accumulation through the activation of signaling pathways whereby it promotes hepatic de novo lipogenesis (11). This lipogenic effect of fructose makes it an unfavorable alternative as it causes oxidative stress, contributing to an inflammatory process, which may accelerate the transition from simple steatosis to NASH and more advanced liver diseases.

CONCLUSION

In conclusion, obesity prevalence has shown an increase in parallel with increased consumption of fructose obtained from diet over the last decades. Excessive fructose consumption, particularly in the form of HFCS has been shown to alter human metabolism, causing metabolic changes that lead to overweight, obesity, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and the formation of fibrosis in the liver which creates the potential to progress to cirrhosis, end stage liver disease or hepatocellular carcinoma.

Studies that point at fructose as one of the culprits behind the development of obesity, also link excessive fructose consumption to the severity of fibrosis, which has been known to be directly associated with the risk of cirrhosis. However, we still need further research in the field to define the precise mechanisms through which a high fructose diet causes NAFLD-associated cirrhosis.

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