High fructose consumption increases liver GLUT-2 expression and the benefits of exercise on the liver metabolism: A literature review

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Abstract

The increase in fructose consumption over the past century is associated with the rising prevalence of metabolic disorders such as obesity, Non-alcoholic Fatty Liver Disease (NAFLD), and insulin resistance. Consuming fructose excessively can exacerbate the detrimental effects of a high-fat diet, resulting in obesity and inflammation. Elevated fructose in hepatocytes also stimulates the expression of lipogenic enzymes, leading to increased hepatic insulin resistance due to lipid accumulation. Intrahepatic insulin resistance conditions trigger an upregulation of hepatic GLUT-2 expression, further worsening metabolic disruptions. Exercise becomes an alternative therapy with positive effects on liver metabolism, including improved insulin sensitivity, reduced lipid accumulation, and glucose homeostasis. The study using a literature review design. The selected articles were sourced from PubMed and ScienceDirect with keywords "high fructose", "GLUT-2", "liver", "exercise", "metabolic disorders", and "insulin resistance". This literature review aims to discuss the mechanism of the high fructose consumption effects on the upregulation of hepatic GLUT-2 expression and the benefits of exercise in improving liver metabolism.

Keywords: High fructose; GLUT-2; Exercise; Liver metabolism; Insulin resistance

1. Introduction

Fructose plays a crucial role in the food industry's production as a sweetener in the form of High Fructose Corn Syrup (HFCS), the majority is found in soft drinks (Stricker et al., 2021). The composition of HFCS-42 consists of 42% fructose, 53% glucose, and 5% oligosaccharides, while HFCS-55 is produced by blending HFCS-42 and HFCS-90 (containing 90% fructose) (Khorshidian, et al., 2021). In low and middle-income countries, there's extensive publicity and urbanization leading to increased consumption of sweetened beverages (Malik et al., 2013). The prevalence of HFCS consumption in the United States increased by nearly 30% from 1970-2000 (Lancaster, 2020). Consuming excessive fructose, more than 50 grams per day, can elevate the risk of obesity, Non-alcoholic Fatty Liver Disease (NAFLD), and insulin resistance (Ter Horst et al., 2017). In the worst cases, NAFLD can progress to more severe liver conditions like Non-Alcoholic Steatohepatitis (NASH) and liver fibrosis (Ter Horst et al., 2017). Glucose transporter 2 (GLUT-2) is a key member of the glucose transporter (GLUT) family, encoded by the solute carrier 2A (SLC2A) gene, commonly found in pancreatic beta cells, hepatocytes, intestines, kidneys, and the central nervous system (Chadt & Al-Hasani, 2020). The expression of hepatic GLUT-2 is regulated by glucose levels and insulin

sensitivity in hepatocytes. Insulin resistance triggers increased GLUT-2 expression in the liver due to disruptions in intracellular mechanisms (Narasimhan et al., 2015). Elevated expression of hepatic GLUT-2 leads to increased fructose absorption by hepatocytes, resulting in an excess substrate production. This negatively impacts metabolic disorders and liver organ damage.

Exercise is still used as a non-pharmacological management due to its numerous benefits in treating various diseases (Hjorth & Febbraio, 2018; Lu et al., 2016). Various forms of exercise can be implemented, such as brisk walking, running, swimming, cycling, ball sports, and weightlifting (Guo et al., 2020). Regular exercise can reduce lipid accumulation in the liver and positively affecting insulin sensitivity (Guo et al., 2020). Improved insulin sensitivity leads to a decrease in hepatic GLUT-2 expression, preventing fructose absorption by hepatocytes. Indirectly, exercise proves beneficial in addressing liver metabolism disorders caused by high fructose consumption.

2. Material and Methods

This research using a literature review design. The selected articles were sourced from PubMed and ScienceDirect using Medical Subject Headings keywords, namely "high fructose," "GLUT-2," "exercise," "liver metabolism," and "insulin resistance". The inclusion criteria for this research are articles published within the last 10 years and using experimental research methods. The exclusion criteria for this study include articles published beyond the past 10 years. Based on a literature search using inclusion and exclusion criteria, 30 selected articles were used in this research.

3. Result and discussion

3.1 The Effect of High Fructose Consumption on Liver GLUT-2 Expression

The absorption of fructose by the liver does not affect insulin secretion, and fructose intake is not regulated by the leptin hormone, which controls satiety (Stanhope, 2015; Taskinen, et al., 2019). This leads to increased fructose consumption, resulting in excess substrate and causing elevated triglycerides through lipogenesis (Stanhope, 2015). Triglycerides are secreted into circulation as Very low-density lipoproteins (VLDL) or stored as lipid droplets (Friedman et al., 2018). Activation of Carbohydrate-responsive element-binding protein (ChREBP), triggered by the accumulation of fructose metabolism products, can downregulate Peroxisome Proliferator-Activated Receptor-α (PPARα), reducing fatty acid oxidation (Hannou, et al., 2018). Excessive fructose consumption can also increase circulating uric acid levels, raising the risk of gout (Hannou, et al., 2018). A study reported that high fructose intake can elevate lactate and inhibit lipid oxidation (Pereira et al., 2017).

Imbalance in fatty acid processing leads to intrahepatic lipid accumulation, generating lipotoxic species such as Diacylglycerol (DAG), ceramides, and Lysophosphatidylcholines (LPC) that trigger oxidative stress and inflammasome activation (Friedman et al., 2018). A study on fructose-induced high-fat diet in mice showed increased lipid accumulation in liver tissues, supporting the activation of proteins associated with the inflammatory process (Jarukamjorn et al., 2016). Another study in mice reported that inflammasome activation in the liver stimulates the expression of pro-inflammatory cytokines like Tumor necrosis factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β), leading to hepatocyte apoptosis (Friedman et al., 2018). Hepatocyte damage results in the release of Reactive Oxygen Species (ROS), contributing to insulin resistance in the liver through c-Jun N-terminal kinase (JNK) and Inhibitor of nuclear factor kappa-B kinase (IKK) activation (Zhang et al., 2020).

In insulin resistance conditions, there is inhibition of Insulin Receptor Substrate (IRS) phosphorylation, leading to increased translocation of Forkhead box protein O1 (FOXO1) to the nucleus, thereby enhancing the expression of gluconeogenic proteins such as Glucose-6-phosphatase (G6Pase) and

Phosphoenolpyruvate carboxykinase (PEPCK) (Perry et al., 2014). Insulin resistance also hinders glycogen formation in the liver by reducing glycogen synthase activity (Perry et al., 2014). Through these mechanisms, hepatic insulin resistance can elevate fasting glucose levels by promoting gluconeogenesis, inhibiting glycogenesis, and contributing to type 2 diabetes (Perry et al., 2014).

In hepatocytes, Glucose Transporter 2 (GLUT-2) is abundant and plays a role in fructose uptake and mediates its release (Chadt & Al-Hasani, 2020). Insulin binding in the liver can lead to a decrease in GLUT-2 hepatic expression, correlating with a reduction in insulin-mediated hepatic glucose production (Eisenberg et al., 2005). This suggests that two transmembrane proteins, insulin receptor (IR) and GLUT-2, interact on the hepatocyte membrane and are internalized into endosomal compartments upon insulin binding (Eisenberg et al., 2005). Insulin resistance can trigger an increase in GLUT-2 hepatic expression through specific mechanisms (Narasimhan et al., 2015). Inhibition of IRS phosphorylation contributes to elevated intracellular glucose production (Perry et al., 2014). When intracellular glucose concentration is higher than plasma concentration, hepatic GLUT-2 is responsible for mediating glucose release from hepatocytes to circulation (Narasimhan et al., 2015). Studies in fructose-induced mice mention that increased hepatic gluconeogenesis can enhance GLUT-2 hepatic expression, aiming to facilitate increased hepatic glucose release (Narasimhan et al., 2015). Ultimately, elevated GLUT-2 expression in the liver worsens metabolic disturbances and can lead to hepatic organ damage due to substrate accumulation produced by fructose.

3.2 The Benefits of Exercise on Liver Metabolism

Here are several articles that discuss the effects of exercise on liver metabolism.

Table 1 List of Articles

NO.	Author	Method	Result
1	(Keating et al., 2015)	True Experimental	Regular low-intensity exercise produces beneficial effects on the reduction of lipid accumulation in the livers of mice.
2	(Simões e Silva et al., 2020)	True Experimental	Moderate-intensity exercise for 8 weeks can enhance liver insulin sensitivity by reducing the levels of Tumor Necrosis Factor-alpha (TNF-α) and increasing the production of another anti-inflammatory cytokine, interleukin-10 (IL-10).
3	(Frantz et al., 2017)	True Experimental	Moderate-intensity treadmill exercise for 8 weeks has been proven to prevent lipid accumulation in the liver through a decrease in triacylglycerol.
4	(Kawanishi et al., 2012)	True Experimental	Exercise for 16 weeks demonstrates the ability to lower levels of Tumor Necrosis Factor-alpha (TNF-α) and fibrosis markers in the liver.
5	(Hsu et al., 2021)	True Experimental	Aerobic exercise for 4 weeks can reduce triacylglycerol (TG) content accompanied by a decrease in lipid accumulation in the liver.
6	(Gunadi et al., 2020)	True Experimental	Moderate to high-intensity exercise induces autophagy, playing a role in reducing liver lipid content through an increase in Fibroblast Growth Factor 21 (FGF21).

7	(Cristina et al., 2021)	True Experimental	Short-term endurance exercise can lower hepatic glucose production, accompanied by increased insulin sensitivity through enhanced Insulin Receptor Substrate (IRS) phosphorylation.

Previous studies have reported that exercise can reduce body weight and decrease the risk of metabolic diseases such as type 2 diabetes, Non-alcoholic Fatty Liver Disease (NAFLD), Cardiovascular disease (CVD), and cancer (Guo, et al., 2020). Physical activity during exercise enhances energy expenditure through physiological processes and cellular mechanisms that accelerate energy breakdown in the body (Petridou, et al., 2018). Exercise can prevent obesity by improving mitochondrial function and fatty acid oxidation (Simões e Silva et al., 2020). During exercise, the liver produces hepatokine Fibroblast growth factor 21 (FGF21), which plays a role in reducing lipogenesis and increasing fatty acid oxidation through the upregulation of the transcription factor Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) (Gonzalez-Gil & Elizondo-Montemayor, 2020). This contributes to reducing lipid accumulation in the liver, resulting in a positive effect on insulin sensitivity (Guo, et al., 2020). Moreover, exercise can also reduce inflammation through the production of anti-inflammatory cytokines (Simões e Silva et al., 2020).

Exercise can generate myokines such as irisin, IL-6, and IL-15 to modulate endocrine activity. Myokine secretion is a response to skeletal muscle contraction post-exercise and other endocrine signals (Gonzalez-Gil & Elizondo-Montemayor, 2020). Myokines can function in autocrine, paracrine, and endocrine ways, influencing tissues like the liver and adipose tissue (Aryana, Hapsari & Kuswardhani, 2018). Interleukin-6 (IL-6) secretion from adipocytes and monocytes is linked to pro-inflammatory responses during infection. However, exercise-induced IL-6 secretion can act as an anti-inflammatory cytokine. Thus, IL-6 can function as both pro-inflammatory and anti-inflammatory depending on its source (Aryana, Hapsari & Kuswardhani, 2018). Serum IL-6 levels have been shown to increase after aerobic exercise, determined by exercise duration (Gonzalez-Gil & Elizondo-Montemayor, 2020). IL-6 plays a role in inhibiting the synthesis of pro-inflammatory cytokines like Tumor necrosis factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β). These myokines also contribute to glucose homeostasis through AMP-activated Protein Kinase (AMPK) activation (Aryana, Hapsari & Kuswardhani, 2018).

Exercise provides various benefits to the liver, including increased fatty acid oxidation, prevention of triglyceride production through the reduction of lipogenic enzymes, inhibition of inflammatory responses, and enhanced insulin sensitivity (Hejazi & Hackett, 2023). As insulin sensitivity in the liver improves, the expression of GLUT-2 in hepatocytes decreases due to internalization into endosomal compartments (Narasimhan et al., 2015). Indirectly, exercise can prevent substrate accumulation resulting from excessive fructose absorption by reducing hepatic GLUT-2 expression.

4. Conclusion

Based on research findings, excessive fructose consumption can lead to increased expression of hepatic GLUT-2 due to insulin resistance and elevated intracellular glucose levels. The heightened expression of hepatic GLUT-2 contributes to substrate accumulation in hepatocytes due to excessive fructose absorption. This can trigger Non-alcoholic Fatty Liver Disease (NAFLD) and insulin resistance. Exercise has been proven to provides various benefits for liver metabolism through the secretion of hepatokines, namely FGF21, which enhances lipid oxidation, and the myokine IL-6, which helps prevent inflammatory responses.

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