



A Review on Effects of High Fructose Diet on Oxidative Stress and Metabolic Syndrome in Male Wistar Rats

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ABSTRACT

Consumption of high fructose is potently related to the development of hypertension and metabolic syndrome. This theory is supported by observational and experimental studies in animals and humans. Rising consumption of fructose has been matched with growing rates of hypertension and hyperglycemia. A high fructose diet has been found to activate vasoconstrictors and inactivate vasodilators. Salt reabsorption a reason for the increase in blood pressure is also shown by excess consumption of fructose. The fructose-taking diet in the rat causes modifications in the triglyceride concentrations in serum, liver TBARS, liver catalase, and SOD activity. In conclusion, the fructose diet caused significant liver damage and a reduction in insulin sensitivity.

Keywords: Fructose, oxidative stress, metabolic syndrome, hypertension.

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INTRODUCTION

The foods which are largely consumed by people nowadays are soft drinks, processed food, sauces, ready-to-serve food, beverages that are a rich source of fructose. ¹ Many fruits and vegetables also contain fructose, a monosaccharide. It is a five-membered ring with a ketone functional group. There are insulin-independent mechanisms involved in the metabolism of fructose which varies from glucose metabolism. The rate-limiting reaction of phosphofruktokinase is diverse in the case of fructose. ² Fructose is inadequate for the insulin-releasing effect and doesn't need insulin for its metabolism. For the last 10-20 years an increase in fructose consumption which is related with an increase in the frequency of obesity and metabolic disorders. ^{2, 3}

As shown in figure 1, the Metabolism of fructose takes place with the help of the enzyme fructokinase which further gets converted into fructose 1- phosphate, after further steps it gets turned into insulin resistance with an increase in the concentration of triglycerides with VLDL.

The role of sex hormones included that, estrogen plays a protective role against high fructose diet in the female rat, testosterone may act as the link between insulin resistance and hypertension hence male rats may be taken for the hypertension study. ²

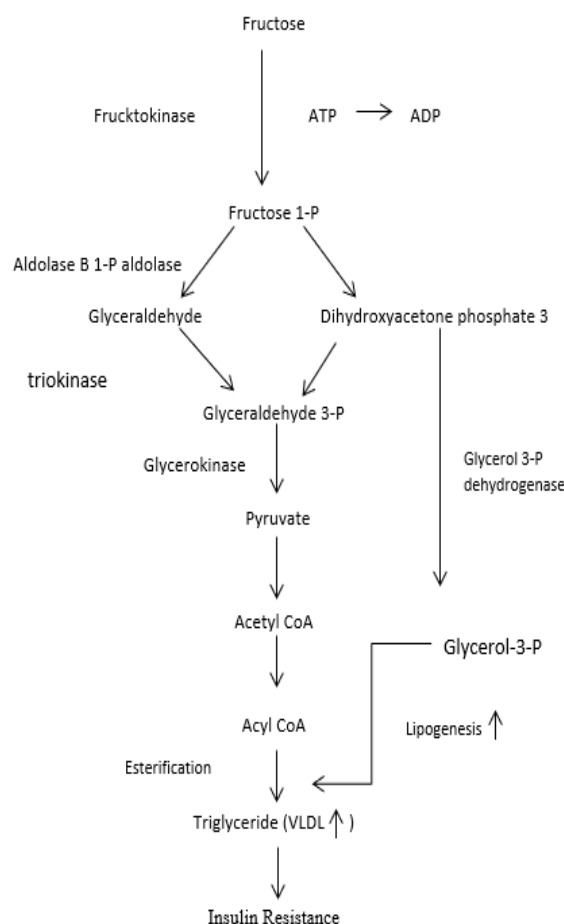


Figure 1: The correlation between fructose metabolism and insulin resistance ³

Metabolic Syndrome

Metabolic syndrome representing obesity, insulin resistance, hypertension, dyslipidemia, etc. can be induced in a high fructose diet. The abnormality of insulin resistance is directly linked to cardiovascular disease like

hypertension in Wistar rats. ² Fructose-enriched diet shows detrimental effects which cause an increase in the reactive oxygen species (ROS) and metabolic abnormalities also known as Syndrome X, which is the factor that contributes to endothelial dysfunction. ¹ The increased hush of NO decreases the production of vasodilators and enhances the production of oxidative stress are correlated.²

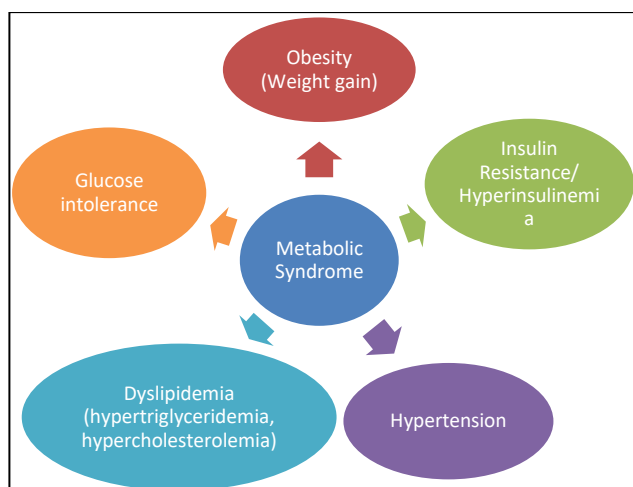


Figure 2: Metabolic Syndrome ⁴

Fructose-taking rats show significantly higher fluid intake as compared to control rats. 10% fructose solution is used instead of drinking water in the case of the fructose treating rats. ⁴ Excess consumption of fructose leads to elevating the serum glucose and serum insulin level in the rats compared to that of control. ⁵ In hyperglycemia, non-enzymatic glycosylation elevates, with the increase in glucose oxidation and catalyzation of these enzymes takes place by Cu^{+2} and Fe^{+2} resulting in the formation of $\text{O}^{\cdot-}$ and OH radicals which may be the reason for cardiac diseases in dyslipidemia. ⁶

A high fructose diet causes an increase in triglyceride concentration. The initiation of the atherosclerotic process in rats is due to modification in the lipid metabolism, and an increase in lipid peroxidation (thiobarbituric acid-reactive substances [TBARS] in the liver) with a reduction in hepatic catalase activity. ^{1, 5} Fatty-acyl-CoA oxidase activity increases in the case of high concentrations of triglycerides in the liver. There is a generation of ROS production by beta-oxidation which is due to the influx of triglycerides into hepatocytes, a reason for anti-oxidant disproportion. The increase in pro-oxidant species causes DNA and membrane damage and disturbance of some regulatory proteins, which enhances tissue inflammation and insulin resistance, apoptosis, cellular mutations, etc. ⁵ In the Liver, chronic fructose consumption causes a lowering in the glucokinase activity and rising in glucose-6-phosphatase activity in the liver, which leads to glycolyzing fructose faster than glucose. ⁷

The mechanism of antioxidants is as follows:

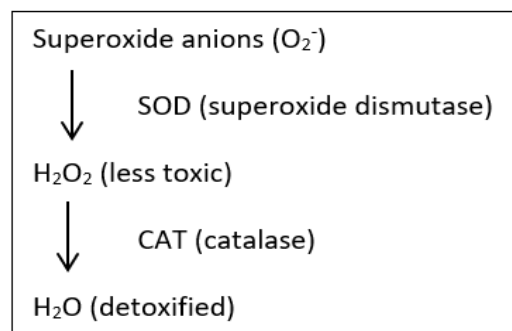


Figure 3: Mechanism of antioxidants in normal conditions⁸

As shown in figure 2, the generated superoxide anions are converted into the less toxic hydrogen peroxide with the help of the enzyme superoxide dismutase, which is further detoxified by catalase into water. Reduction in the SOD activities is observed in high fructose diet rats which show hepatic vulnerability to oxidative stress.

The insulin resistance/ hyperinsulinemia takes place due to sodium retention in the rats. Impairment of antioxidant defenses in the liver of fructose-treated rats is due to the high salt present in the body, in this case, renal sodium reabsorption generates oxidative stress. ⁸ The lowering of insulin sensitivity was associated with hyperglycemia and hyperinsulinemia. ⁷

A cytokine i.e. Leptin is produced from the ob gene which is secreted by adipose tissue. Leptin shows its action by suppressing application and enhancing energy expenditure. A high fructose diet causes hyperleptinemia in rats with an increase in insulin levels and body weight enhancement. In adipocytes, leptin production and gene expression is increased due to insulin. ⁹ An example of an adipokine is Adiponectin which regulates the metabolism of glucose and lipid in the cardiac muscle, skeletal muscle, and liver. This hormone also maintains food intake, glucose uptake, fatty acid oxidation, depletion of glycogen synthesis and triglycerides content, etc. A decrease in the level of adiponectin in serum can be a cause of metabolic syndrome and insulin resistance. ¹⁰

The mechanism for Hypertension

In the development of hypertension in fructose-treated rats, there is some role of androgens. The essential and prior part of hypertension in fructose-consuming rats showed sympathetic hyperactivity and after on metabolic consequences to the sympathetic nervous system-induced insulin resistance. Fructose-induced hypertensive rats are indicated by the increase in total mesenteric vascular endothelin-1 content and change in arterial reactivity to endothelin-1. ¹¹

Fructose consumption causes an increase in sodium absorption in the intestine, by inhibiting systemic endothelial function, and by stimulating the sympathetic nervous system. ¹²

The probability of occurrence of hypertension and stroke is due to a decrease in potassium intake. Consuming the high fructose diet causes an increase in VLDL synthesis, which contains 10-20% cholesterol and triglycerides transportation in the liver, with the rise in the cholesterol concentration.¹³

Endothelial Dysfunction

Endothelial Cells produce relaxing and contracting factors by controlling vascular tone. Fructose diet elevates the circulating insulin and fructose metabolites, which modify the endothelial activity. Examples of factors are nitric oxide i.e. Vasodilators, Angiotensin-II, Endothelin-1, Thromboxane A2, are some Vasoconstrictors.¹⁴

Elevating the catecholamine levels by a high fructose diet is the reason for endothelial dysfunction. Nitric oxide prevents the release of norepinephrine, by increasing its vasodilatory action are shown by some studies.¹⁴

Plasma uric acid concentration

Fructose is phosphorylated to fructose-1-phosphate to induce ATP hydrolysis to AMP and then to the formation of uric acid.¹⁵ The bioavailability of nitric oxide is inhibited by fructose intake and also elevates uric acid concentration i.e. hyperuricemia, glucose uptake occurs in presence of insulin with the help of nitric oxide. Insulin resistance and hypertension occur due to a decrease in nitric oxide bioavailability by uric acid.¹⁶

Reasons for the atherosclerotic process are due to worsening and starting of endothelial dysfunction which is commonly accepted. In the primary stage of atherosclerosis, endothelial cell activation by several inflammatory stimuli results in increased expression of adhesion molecules on the endothelial surface. In North Americans, there are chances of diabetes-related death are 65-80% in the case of atherosclerosis and an individual with diabetes has a 2- to 4- fold more risk of mortality from coronary artery disease (CAD).¹⁷

Table 1: Literature survey on oxidative stress and metabolic syndrome in fructose treated rats.

Sr. no.	Author, Journal, Year	Observations
1	Aurelle Girard, et.al. Elsevier, Nutrition 22 (2006) ¹	Fructose feed negatively affects antioxidant capacity in the blood of hypertensive rats but improves this capacity in the liver.
2	Linda T. Tran, et.al. Mol Cell Biochem (2009) ²	Increased formation of ROS and elevated levels of uric acid contribute to fructose-induced hypertension.
3	LI Jian- Mei, et.al. Chinese Journal of Natural Medicines (2008) ⁹	Quercetin and rutin, allopurinol reduced hyperleptinemia, hyperlipidemia, hyperinsulinemia in fructose-fed rats.
4	SOK Kuan WONG, et.al. Sains Malaysiana (2019) ¹⁰	Leptin, adiponectin, insulin controls the energy balance tightly during metabolic syndrome.
5	Marek Kretowicz, et.al. SAGE-Hindawi, International Journal of Nephrology (2011) ¹²	Excess intake of fructose results in obesity, diabetes, cardio-renal disease.
6	Alice Victoria Klein, et.al. Journal of Hypertension (2015) ¹⁴	Excess fructose causes activation of vasoconstrictors, inactivation of vasodilators, metabolic disorders, Endothelial dysfunction.
7	Julie Dupas, et.al. Hindawi, BioMed Research International (2017) ¹⁵	Fructose supplementation for long-term induced metabolic syndrome (hypertension, insulin resistance, dyslipidemia).
8	JIN- BO LIU, et.al. Molecular Medicine Reports (2009) ¹⁷	Protective effect of adiponectin with reduced activity of various inflammation-related factors.
9	Jerrrome Busserolles, et.al. British Journal of Nutrition (2002) ¹⁸	High fructose consumption affects the balance of free radical production and antioxidant defense in rats, increases lipid susceptibility to peroxidation.
10	Carole Oudot, et.al. Kidney International (2013) ¹⁹	Sodium restriction diet shows favorable effects in renal and metabolic alterations linked with a high-fructose diet in rats.
11	Harish Vasudevan, et.al. American Journal of Physiology-Heart and Circulatory Physiology (2006) ²⁰	The rise in blood pressure with endothelial dysfunction is prevented by gonadectomy in male rats.
12	Soter Dai and John H. McNeil, Journal of Pharmacological and Toxicological Methods, Elsevier Science Inc. (1995) ²¹	10 % Fructose solution in drinking water in Wistar rats associated with hyperinsulinemia, hyperglycemia, hypertriglyceridemia.

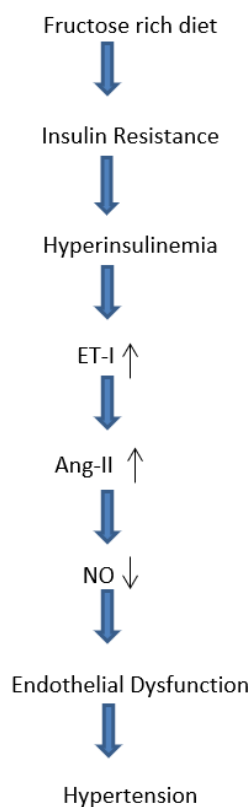


Figure 4: Fructose administration causes endothelial dysfunction which can lead to hypertension after several pathways. ET-1, endothelin-1; NO, nitric oxide; Ang II, Angiotensin II¹⁴

CONCLUSION

In conclusion, the experimental and epidemiological studies were directed to advise a link between excess fructose consumption and hypertension. High fructose consumption has shown deleterious effects such as impaired glucose tolerance, insulin resistance, dyslipidemia, and endothelial dysfunction. There is a change in the oxidative stress also shown by the excess fructose-consuming rats.

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