

Fructose-Induced Insulin Resistance: Prospective Biochemical Mechanisms

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ABSTRACT

Increased intake of dietary fructose is markedly associated with multiple negative health outcomes and burdens. Insulin resistance (IR) and type 2 diabetes mellitus (T2DM) are the most common complications that present with conjugated cellular-biochemical abnormalities. This article explains the involvement of increased dietary fructose intake in the occurrence of IR and T2DM and addresses basic metabolic mechanisms. PubMed, Medline, Science Direct, ADI, and WHO databases were searched through June 2021. Current research predicts that over 350 million people may have diabetes by 2030. IR acts as an influencer promoter of T2DM development. IR can occur as a result of high fructose intake. Fructose metabolism results in de novo lipogenesis, while its decreasing effect of peroxisome proliferator-activated receptor (PPAR) activity elevates the levels of inflammatory cytokines, resulting in down-regulation of insulin receptor substrate-1 phosphorylation. Fructose stimulates oxidative stress by activating nicotinamide adenine dinucleotide phosphate oxidase and synthesis of advanced glycation end-products. Fructose also stimulates the purine-induced uric acid synthesis and leptin resistance, which contributes to abnormal insulin action. It is crucial to understand the mechanisms of fructose-induced IR via induction of oxidative stress, inflammation, leptin resistance, and uric acid production. This helps prevent and control variable diseases, T2DM being the most.

Keywords: Cytokines, Fructose, Inflammation, Insulin resistance, Leptin, Oxidative stress, Type 2 diabetes mellitus, Uric acid.

INTRODUCTION

Recent data indicate that over 218 million individuals suffer from Type 2 diabetes mellitus (T2DM) worldwide, while over 350 million people are predicted

to be diabetics by 2030 (Saeedi et al., 2019). T2DM is a progressive, chronic disorder that is characterized by insulin resistance (IR) as a primary condition that results in partial pancreatic cell failure (Zatterale et al., 2020; Ahmad et al., 2020a). High fructose intake induces IR and its metabolic abnormalities (Hu et al., 2017). Fructose is a simple sugar derived from sucrose that is a major staple food worldwide and consists of 50% fructose and 50% glucose (Lozano et al., 2016). Gut sucrase hydrolyzes

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dietary sucrose releasing free fructose and glucose to be readily absorbed later (Veedefald et al., 2019).

Around 50–75% of fructose metabolism occurs in the liver and minorly in the kidneys and adipocytes (Zwarts et al., 2019). After ATP consuming phosphorylation step catalyzed by fructokinase to fructose-1-phosphate, fructose absorption occurs via particular intestinal transporters. Fructose absorption or cell uptake requires glucose transporter-5, glucose transporter-2, and supposedly solute carrier family 2, which are predominantly found in the liver, intestinal epithelium, kidney proximal tubule, adipocytes, and vascular endothelium (Eberhart et al., 2020; Koepsell, 2020). Fructose is minorly metabolized by the hexokinase pathway due to its higher Michaelis constant (K_m) values than glucose (Sharma et al., 2020), while both hexokinase and phosphofructokinase prevent excessive phosphorylation (Huang et al., 2016; Buziau et al., 2020). Low concentrations of fructose significantly diminish the levels of ATP in vascular endothelial cells and human proximal tubular cells, which inhibit protein synthesis, initiate inflammatory protein production and response, activate endothelial dysfunction, and promote oxidative stress (Mai and Yan, 2019; Simons et al., 2020). Fructose is considered a lipogenic nutrient, as it stimulates triglyceride synthesis and activates hepatic fat cell deposition (Federico et al., 2021). This process is mediated by increased levels of fatty acyl-coenzyme A and di-acylglycerol, resulting in greater hepatic triglycerides production and apolipoprotein B levels (Al-Jawadi et al., 2020; Federico et al., 2021).

Fructose stimulates the production of excess uric acid (Zhang et al., 2017). Since ATP is extensively consumed during fructose metabolism, AMP molecules accumulate, stimulating AMP deaminase leading to uric acid production and an abnormally elevated serum uric acid level (Iskender et al., 2021). This article describes and discusses some noteworthy mechanisms by which

fructose promotes and accelerates the occurrence of IR and T2DM as serious metabolic consequences.

LITERATURE SEARCH

An up-to-date literature search was conducted on the link between dietary fructose intake, IR, and T2DM, focusing on the basic biochemical mechanisms. The search was limited to the most recent English publications covering the last 5 years (2016–2021). Relevant articles were principally identified through an online search of PubMed, Medline, Science Direct, ADI, WHO databases, and PsycINFO. Google Scholar and other databases were also used. Included articles were mainly *in vivo* and *in vitro* original experimental, clinical, intervention, and cross-sectional researches. Some researches in animals and review articles were also consulted. For further search accuracy, the reference lists of works were checked for additional publications from the major databases.

FRUCTOSE-INDUCED LIPOGENIC POSTURE

The high-fructose-diet ($\geq 60\%$ fructose) is known to increase hepatic cell lipids. When this diet is provided sustainably, it induces hepatic abnormality, extrahepatic IR, and steatosis (Higgins et al., 2018). Fructose increases *de novo* lipogenesis by increasing hepatic triglyceride (TG) formation and limiting the oxidation of fatty acids (Beysen et al., 2018). This occurs by elevation of hepatic concentrations of Acetyl-CoA, which leads to posterior multiplied Malonyl CoA overproduction as lipogenesis intermediate by which acetyl CoA is added to fatty acids of long-chains. This process inhibits the oxidation of fatty acid via the prevention of its entry into the mitochondria (Geidl-Flueck et al., 2021).

Independently of insulin, fructose activates sterol regulatory element-binding proteins, which stimulates *de novo* lipogenesis involved genes (Gugliucci, 2016). The secreted very-low-density lipoprotein-TG is donated into the systemic circulation to elevate the levels of circulatory fatty acids (García-Arroyo et al., 2019; Todoric et al.,

2020). As apolipoprotein B-100 is substantial for TG-very-low-density lipoprotein intracellular assembly, apolipoprotein B-100 decomposition is minimized when hepatic lipid is increased. This accumulates apolipoprotein B in the hepatic-endoplasmic reticulum and causes endoplasmic reticulum stress that can promote sterol regulatory element-binding proteins and carbohydrate response element-binding protein activation; a matter which contributes to de novo lipogenesis by the activation of fatty acid synthase, acyl coenzyme-A carboxylase, and stearoyl coenzyme-A desaturase-1 lipogenic genes expression which enhances the lipogenic status (Unsal et al., 2020). The boosted sterol regulatory element-binding proteins-c expression by fructose supplementation leads to hepatic insulin signaling suppression resulting in glucose intolerance and hepatomegaly, while excessive fructose intake enhances the elevation of hexose-phosphate levels in the liver, which promotes carbohydrate response element-binding protein activation, resulting in hypertriglyceridemia and hyperinsulinemia (Lehti et al., 2018; Jones et al., 2020).

In adipocytes, signaling abnormalities stimulate TG stores lipolysis and non-esterified fatty acids efflux into the bloodstream, which augments the problem (Xie et al., 2020). Extrahepatic tissue exposure to massive concentrations of non-esterified fatty acids negatively reduces insulin sensitivity, as the intramyocellular lipid content increases; this reduces the circulating lipids uptake and stimulates the stored TG hydrolysis, which raises free fatty acid levels in the blood, reduces glucose uptake by muscles, and increases liver glucose production (Morigny et al., 2021; Selen et al., 2021). As a result, high levels of blood glucose are shown with severe lipotoxicity in conjugation with pancreatic cell death. To compensate for this, the pancreatic cells keep increasing in mass and insulin secretion, resulting in unbeneficial hyperinsulinemia that ends by hyperglycemia, pancreatic islet cell loss, and T2 D (Jung and Bu, 2020; Ahn et al., 2020).

Hepatic and myocytic intracellular IR mechanism usually occurs via the induction of novel-protein kinase-C by its activator, the diacylglycerol (Kang and Chiang, 2020). Novel-protein kinase C activation causes a severe depletion in insulin receptor substrate 1 (IRS1) level of phosphorylation and its tyrosine, which results in a reduction of glucose transporter activity to end by reduced intracellular glucose uptake. Additionally, diacylglycerol raised levels also activate kinases of serine/threonine, such as inhibitory kinase and nuclear factor-B (Gupta et al., 2021). Accordingly, fructose-induced IR and its conjugated hyperlipidemia interfere with insulin signaling and activate the pro-inflammatory floods that lead to aggravated IR. Figure 1 presents the biochemical mechanisms of fructose-induced insulin resistance.

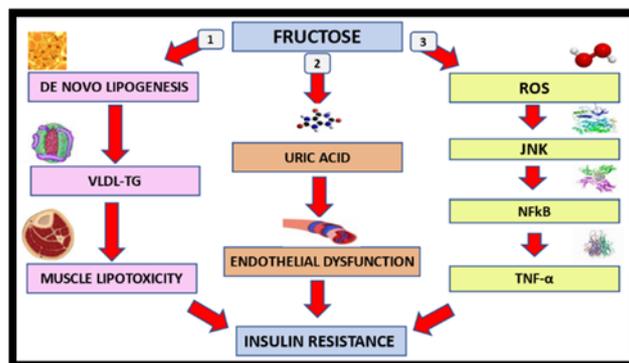


Figure1. Biochemical mechanisms of fructose-induced insulin resistance

[Abbreviations: VLDL: very-low density lipoprotein; TG: triglyceride; ROS: reactive oxygen species; JNK: c-Jun N-terminal kinase; NFκB: nuclear factor kappa B; TNF-α: tumor necrosis factor-alpha]

FRUCTOSE-INDUCED INSULIN ESISTANCE: THE ROLE OF INFLAMMATORY SIGNALING

Low-grade inflammation is considered a basic metabolic abnormality observed in IR (Mansyur et al., 2020). Increased fructose-induced adipose tissue mass strongly contributes to tumor necrosis factor-α over-release (Caputo et al., 2017). Tumor necrosis factor-α-

mRNA expression is observed increasingly in hepatic tissues, while inflammatory pathways activation that is done by fructose feeding influence the secretion of lipoproteins out of hepatic and intestinal tissues (Cigliano et al., 2018). In the liver and intestine, high levels of tumor necrosis factor- α result in decreased insulin receptors intracellular tyrosine phosphorylation, protein kinase B, and IRS-1 signaling pathway which elucidates in decreased insulin sensitivity leading to the accretion and increase of apolipoprotein B-containing chylomicron particle production (Qu et al., 2018; Alipourfard et al., 2019).

The nuclear factor of *kappa* light polypeptide gene enhancer in B-cells kinase and nuclear factor kappa light chain enhancer of activated B cells are inflammatory markers that are activated by tumor necrosis factor- α and interleukin 6, as both can down-regulate the phosphorylation IRS-1 in opposition to the normal healthy status where insulin attaches to its receptor resulting in receptors auto-phosphorylation of IRS on tyrosine residues which activate several variables of second messenger proteins as intracellular signaling cascade complex that involves protein kinase B that results in positive stimulation of the glucose uptake into the cells (Hong et al., 2017; Rai et al., 2019; Sanvee et al., 2019).

Activation of protein kinase C (PKC) minimizes insulin-stimulated glucose- uptake, which elevates tyrosine phosphorylation level (phosphatidylinositol 3-kinases (PI 3-kinase)) activity of insulin receptor (Ganesan et al., 2018). Thus, inappropriate activation of PKC promotes phosphorylation of IRS-1 serine/threonine, resulting in the prevention of protein phosphorylation for tyrosine that is necessarily essential for normal intracellular insulin-signaling- pathway (Gassaway et al., 2018).

PKC is primarily associated with lipid-induced IR too. The incidence of hepatic IR is correlated to the increased de novo lipogenesis as a yield of diacylglycerol and novel

PKC (Katsuyama et al., 2019; Ali et al., 2020). Chronic high fructose consumption down-regulates the gene of the insulin receptor, which abnormalizes insulin at the intracellular level of myocytes and hepatocytes by IRS-1 weak phosphorylation and phosphatidylinositol 3-kinase decreased activity, which is considered as a second possible IR molecular mechanism (Marunaka, 2018; Oyabambi et al., 2020). Conclusively, the mechanisms that lay behind fructose-induced IR are reduction in the number of insulin receptors or decreased phosphorylation or both.

As insulin sensitivity reduction is majorly due to reduced mitochondrial fatty acid oxidation and increased hepatic diacylglycerol accumulation, which abnormally activates PKC resulting in insulin signaling inhibition (Rehman et al., 2020). This suggests that fructose modulates the stimulation of de novo lipogenesis via co-activating the peroxisome proliferator-activated receptor (PPAR) and nuclear respiratory factor. PPAR has a key role in controlling the encoding genes of dehydrogenase transcription, which are long-chain- acyl-coenzyme A and -medium-chain- acyl-coenzyme-A (Rehman et al., 2020). Diminished PPAR activity settles the mitochondrial oxidation of fatty acid, where the hepatic accumulation then induces oxidative stress with observed increased activity of pro-inflammatory nuclear Factor-B transcription (Gong et al., 2021).

FRUCTOSE-INDUCED INSULIN RESISTANCE: THE ROLE OF OXIDATIVE STRESS

Insulin resistance is related to free radicals generated by increased oxidative stress; likewise, the use of fructose enhances oxidative stress, as it increases inflammatory markers production and hydrogen peroxide output (Abolghasemi et al., 2020, Ahmad et al., 2020a & b; Farah et al., 2020). As convincing evidence, when fructose-fed rats are treated with antioxidants, a reduced reactive oxygen species production is detected with IR avoidance (Ahmad et al., 2020a and b). Since oxidative

stress and inflammation are linked to insulin resistance through shared pathways, like c-Jun NH₂-terminal kinase-1, both stimuli are crucial to consider when consuming fructose (Lawan et al., 2018; Maguiña et al., 2020). The excessive production of reactive oxygen species is also based on nicotinamide adenine dinucleotide phosphate oxidase activation; and the former results in raised oxidative stress response, as demonstrated by increased plasma reactive oxygen species levels and urinary thiobarbituric acid reactive substances (Jeong et al., 2018; Aguilar et al., 2020; Kim et al., 2020).

The polyol pathway is a major contributor to fructose-enhanced oxidative stress. In fructose metabolism, fructose-3-phosphate is converted to oxoaldehyde, which reacts with monoacids to form advanced glycation end products (Qais et al., 2019). Schiff base adducts are formed by the interaction of D-fructose with the N-terminal amino-acid of proteins and/or -amino groups (Do Koo et al., 2019). The result of this reaction is known as a Heyns rearrangement (using carbon 2 instead of carbon 1 of the hexose), then glycation products are formed, and then rearranged, dehydrated, and condensed to form advanced glycation products (Rodrigues et al., 2017). Massive amounts of advanced glycation end products expose cells to oxidative stress and decrease antioxidant cellular defenses resulting in the generation of oxidant species and elevating levels of oxidative stress that directly contributed to IR and T2DM incidence (Ahmad et al., 2020 a & b; Farah et al., 2020).

FRUCTOSE-INSULIN RESISTANCE: THE ROLE OF LEPTIN

Leptin is a well-notarized adipose-released hormone. It has both; central and peripheral effects on the biochemical and physiological behavior of the body against nutrients intake (Qais et al., 2019). Leptin receptors and their performance play an essential role in different metabolic abnormalities that include severe

obesity, aggravative hepatic steatosis, and intensive IR (Gugliucci, 2017; Deo et al., 2020; Ahmad et al., 2020a).

Acute fructose feeding decreases leptin secretion, while glucose metabolism regulates leptin release; this phenomenon is likely to be associated with weak insulin response to fructose consumption (Sanchez-Lozada et al., 2019). On the other hand, chronic fructose feeding that extends at least four weeks induces hyperleptinemia and exhibits leptin resistance with lowered insulin sensitivity, hepatic steatosis, and high levels of circulating TG in humans and animals (Zhang et al., 2017). These conflicting responses display a difference between acute and chronic fructose intake, where chronic consumption of fructose develops leptin resistance and hyperleptinemia due to the increased mass of adipose tissue, which promotes leptin resistance and its over release (Baena et al., 2016). The proposed biomolecular pathway of leptin resistance involves the suppressor signaling molecule of cytokine signaling 3, as fructose intake induces the expressions of this suppressor and impairs the phosphorylation pathway of serine/threonine, which results in leptin resistance (Sigala et al., 2020). Also, fructose prompts protein tyrosine phosphatase-1B expression, exhibits c-Jun NH₂-terminal Kinase signaling pathway impairment, and intracellular mitogen-activated protein kinase signaling inhibition that increases forkhead box protein O1 expression due to suppressor signaling molecule of cytokine signaling 3 hyper-expression (Lanaspa et al., 2018).

Leptin induces oxidative metabolic reactions of fatty acids by the induction of PPAR activation via the AMP-activated protein kinase action (Sangüesa et al., 2018). Consecutively, a decrease in PPAR activation occurs, which stimulates impaired oxidation of fatty acids that strongly contributes to hepatic TG accumulation, while contrarily, the activation of PPAR_ reversed leptin resistance conditions. Activation of protein phosphatase-2A is another consequence that contributes to leptin

signaling impairment and further metabolic diseases (Bartley et al., 2019).

FRUCTOSE-INDUCED HYPERURICEMIA

Fructose raises uric acid in humans and rodents (Liu et al., 2021). After fructose ingestion, fructokinase phosphorylates fructose in hepatocytes, while ATP serves as a phosphate donor. ADP is generated and then metabolized into a variety of purine substrates. Meanwhile, the gradual depletion of phosphate during these reactions activates AMP deaminase, and the combination of the increased substrate via fructose and AMP deaminase enzyme activation upregulates urate development (Figure 2). Finally, the resultant accumulative uric acid fragment production introduces its prooxidant behavior extensively (Xu et al., 2019; Bernardes et al., 2017; Furuhashi, 2020). Uric acid is a prooxidant that produces reactive oxygen species through a variety of mechanisms, including interactions with peroxy-nitrite and oxidized lipids (Egea et al., 2020). These reactive oxygen species elevate the oxidative stress level and stimulate the activating conditions that promote IR (Kurajoh et al., 2021).

Uric acid high levels promote severe endothelial dysfunction, which leads to a crucial decrease in reduced endothelial nitric oxide bioavailability. This is due to endothelial nitric oxide synthase deficiency, which develops insulin resistance and hypertriglyceridemia (Mehmood et al., 2020). Therefore, high fructose intake may cause a rapid increase in serum uric acid, which lessens endothelial nitric oxide bioavailability and inhibits insulin-mediated nitric oxide release leading to slow rates of glucose delivery to skeletal muscles (Hotta et al., 2020; Oyabambi et al., 2020).

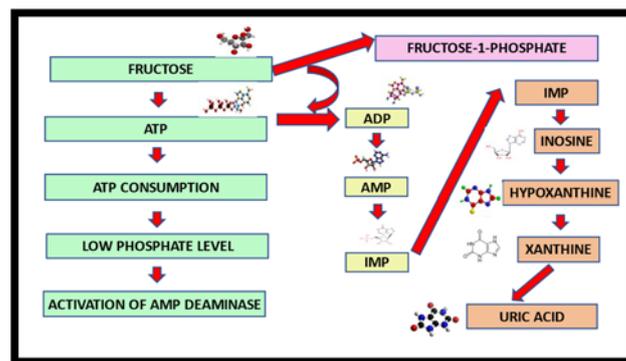


Figure 2. The pathway of fructose-induced hyperuricemia

CONCLUSIONS

Taken together, the present article addresses the possible detrimental effects of high fructose intake, including the fructose-stimulated molecular mechanisms with conjugated biochemical pathways. Fructose markedly stimulates de novo lipogenesis that results in hyperlipidemia and the activation of particular intracellular signaling pathways that promotes oxidative stress. Inflammation induction through the production of inflammatory cytokines is substantially conjugated with abnormal intracellular signaling pathways and insulin-receptor binding mechanisms. Uric acid hyperproduction and leptin resistance due to high leptin release play a key role in the development of IR and T2DM at the molecular stage by their reactive role in oxidative stress and pro-inflammation status induction. However, further investigation is needed to gain an in-depth understanding of the inhibition or disruption of fructose metabolism that can prevent its complications and potentially lead to innovative solutions for the prevention and treatment of chronic fructose-induced disorders, which may change the healthcare landscape of fructose-induced IR and T2DM.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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مقاومة الأنسولين المحفزة بالفركتوز: الآليات الكيميائية الحيوية المحتملة في الأردن

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ملخص

ترتبط زيادة تناول الفركتوز الغذائي بشكل ملحوظ بالعديد من النتائج والأعباء الصحية السلبية. وتعد مقاومة الأنسولين (IR) وداء السكري من النوع الثاني (T2DM) أكثر المضاعفات شيوعاً والتي تظهر مقترنة مع التشوهات الخلوية والكيميائية الحيوية. وتشرح هذه المقالة تورط زيادة تناول الفركتوز الغذائي في حدوث IR و T2DM، وكذلك تتناول آليات التمثيل الغذائي الأساسية. وتم البحث في قواعد بيانات PubMed و Medline و Science Direct و ADI و WHO حتى حزيران 2021. وتتوقع الأبحاث الحالية أن أكثر من 350 مليون شخص قد يعانون من مرض السكري بحلول عام 2030. وتعمل IR كمسبب مؤثر لحدوث T2DM. ويمكن أن تحدث IR نتيجة تناول كميات كبيرة من الفركتوز. وينتج عن استقلاب الفركتوز تكوين الدهون، في حين أن تأثيره المتناقض لنشاط مستقبلات تنشيط البيروكسيسوم يرفع مستويات السيستوكينات الالتهابية، مما يؤدي إلى التنظيم المنخفض لمستقبل الأنسولين للفسفرة-1. ويحفز الفركتوز الإجهاد التأكسدي عن طريق تنشيط النيكوتيناميد الأدينين ثنائي النوكليوتيد أوكسيداز الفوسفات وتوليف المنتجات النهائية المتقدمة للجلوزه. ويحفز الفركتوز أيضاً كل من تخليق حمض البوليك الناتج عن البيورينات ومقاومة اللبتين، مما يساهم في حدوث خلل في عمل الأنسولين. ومن الأهمية بمكان فهم آليات IR التي يسببها الفركتوز عن طريق تحريض الإجهاد التأكسدي والالتهاب ومقاومة اللبتين وإنتاج حمض البوليك. ويساعد فهم هذه الآليات في الوقاية من الأمراض المتغيرة والسيطرة عليها، ويعتبر T2DM من أكثرها.

الكلمات الدالة: السايوتوكين، الفركتوز، الالتهاب، مقاومة الأنسولين، اللبتين، الإجهاد التأكسدي، داء السكري من النوع 2، حمض البوليك.

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