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The possible mechanisms of high-fructose diet-induced pancreatic disturbances

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ABSTRACT: Excess fructose consumption in the regular human diet causes several health problems. The main source of dietary fructose is sugar-sweetened beverages, which are especially consumed by children and teenagers. High-fructose intake is one of the major responsible factors of the increased prevalence of metabolic syndrome and type 2 diabetes worldwide. The dietary high-fructose-induced metabolic syndrome was evidenced by hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertension, fatty liver disease, central adiposity, and inflammation. Molecular findings indicated that there was a suppression of insulin signaling and activation of oxidative stress in different tissues including the liver, blood vessels, adipose tissue, and kidney in the excess intake of fructose. However, there is a limited mechanistic study on the pancreatic disturbances induced by dietary high-fructose. The hyperglycemic condition in the consumption of high-fructose may lead to morphologic and pathological changes to increase the capacity of insulin secretion in the pancreas. High-fructose can activate the mitogenic and apoptotic pathways, thus probably inducing hyperplasia in β-cells. The overactivation of β-cells can trigger oxidative and endoplasmic reticulum stress as well as inflammation in the pancreas. In conclusion, high-fructose consumption may cause pancreatic disturbance possibly through stimulation of cellular oxidative stress, inflammation, mitogenesis, and apoptosis. Pancreas is one of the first organs affected by metabolic abnormalities, therefore, elucidation of potential mechanisms underlying high-fructose diet-induced pancreatic pathologies would be valuable in the prevention and treatment of the metabolic syndrome as well as type 2 diabetes.

KEYWORDS: Dietary fructose; pancreas; hyperglycemia; cellular stress; inflammation.

1. INTRODUCTION

Metabolic syndrome is defined as a cluster of conditions, including hyperlipidemia, hyperinsulinemia, central adiposity, hypertension, chronic low-grade inflammation, and fatty liver disease. Animal and human studies have indicated that excess intake of fructose, which is an important component of the current human diet, causes metabolic syndrome [1, 2]. Fructose is a monosaccharide naturally found in fruits, vegetables, and honey, also it is commonly added to soft drinks and ready-to-eat foods in the form of high-fructose corn syrup or sucrose. High consumption of sugar-sweetened soft drinks, particularly in childhood, adolescence, and young adulthood, is one of the major causes of the increasing prevalence of metabolic diseases worldwide. According to reports from the International Diabetes Federation, type 2 diabetes (T2D) has affected 537 million adults globally in 2021, and this account is estimated to reach 784 million in 2045 [3]. T2D, a chronic hyperglycemic status, is characterized by hyperinsulinemia and peripheral insulin resistance, especially in skeletal muscle, adipose tissue, and liver. Particularly, the suppression of hepatic insulin signaling was associated with dyslipidemia and hypertriglyceridemia in metabolic disorders [4]. Moreover, the inflammation in the adipose tissue promotes insulin resistance through macrophage-derived inflammatory cytokines [5]. Hyperinsulinemia is the first indication of metabolic abnormality in the pancreatic tissue. Pancreatic β-cells enhance the capacity of insulin secretion with islet cell hyperplasia to compensate the hyperglycemia. The increased secretory activity in the β-cells can cause the activation of several pathological processes such as cellular stress, inflammation, and mitogenesis [6, 7]. However, the mechanisms of the pathological changes induced by hyperinsulinemia and also hyperglycemia in the pancreas are not well understood. Regarding diet-induced metabolic disorders, studies conducted in our laboratory showed that a

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high-fructose diet elevated plasma insulin level and suppressed insulin signaling in hepatic, vascular, adipose, and renal tissues [8,13]. Additionally, dietary fructose intake has led to increased lipogenic gene expression in the liver and adipose tissue of rats [11, 12, 14]. A fructose-rich diet was also shown to enhance the expression of inflammatory cytokines and macrophage infiltration in different tissues including liver, testis, kidney, ileum, and adipose tissue [10, 12, 14-16]. In the pancreatic tissue, high-fructose-induced hyperglycemia may lead to the activation of cellular stress and mitogenic pathways thereby leading to a high secretion capacity of β-cells. Dietary fructose may also trigger pancreatic inflammation and β-cell death during the disease progression [17, 18]. Thus, dietary fructose may cause structural and functional disturbances in β-cells. However, there is a limited mechanistic study on the pancreatic irregularities in fructose-induced metabolic syndrome. A better understanding of the mechanism of high-fructose-induced pancreatic disturbances could provide novel insights for potential drug targets. In this review, we discussed the possible mechanisms underlying high-fructose diet-induced pancreatic pathologies.

2. THE EFFECTS OF HYPERGLYCEMIA ON β-CELL MORPHOLOGY

The progression of insulin resistance in T2D remains poorly understood but evidence implicates a failure of pancreatic β-cells to overcome the insulin resistance, thereby leading to chronic hyperglycemia. Insulin resistance causes various structural changes in the endocrine pancreas and functional disorders in β-cells [19]. In the prediabetic state, pancreatic β-cells increase insulin secretion to compensate the increased blood glucose levels. In the following period, this compensation is not enough to normalize the blood sugar and glucose level is increased despite hyperinsulinemia. Moreover, the hyperinsulinemic status is accompanied by a suppression of insulin signaling in the target tissues for insulin, including skeletal muscle, adipose tissue, and liver. In the early period of T2D, β-cells initially increase secretory capacity to meet the increased insulin requirement. In the later periods, it was observed an increase in the apoptosis of β-cells, which triggers the cells to lose their functional capacity. This condition induces a decline in islet mass and a change in its architecture [20]. Likewise, studies show that the chronic hyperglycemic situation causes an increase in the requirement for insulin, thereby leading to overstimulation of β-cell and the development of insulin resistance [21]. In addition, hyperglycemia triggers inflammation and thus generates changes in the composition of the extracellular matrix [22, 23]. The inflammatory status is thought to produce functional impairment in β-cells, resulting in impaired insulin secretion in the late period of T2D [24-26]. The prediabetic condition, which occurs as a result of high-fructose consumption, may lead to a similar process on the pancreas.

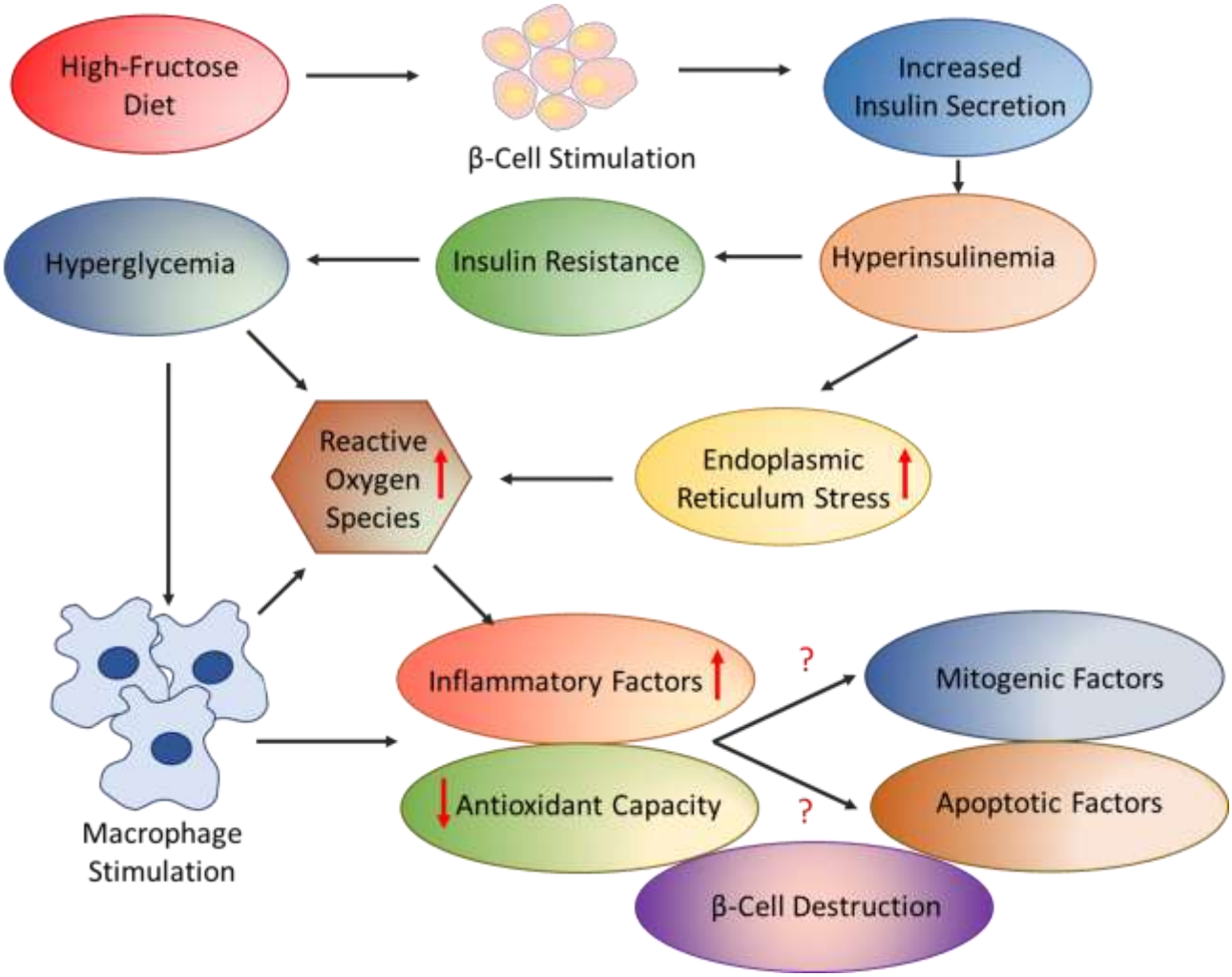
3. THE EFFECTS OF HIGH-FRUCTOSE DIET ON MORPHOLOGICAL ALTERATIONS IN THE PANCREAS

Several studies have demonstrated that excess fructose intake causes hyperinsulinemia [12, 13, 15]. However, the mechanisms underlying high-fructose-induced functional and pathological alterations in the pancreas are still being investigated. In rats fed high-sucrose/high-fat diet, it was shown that the pancreatic islet diameter increased until the 24th week but decreased in the following periods [27]. In another study, it was reported that dietary fructose increased the number and mass of pancreatic islets [28]. Furthermore, excessive fructose consumption has been demonstrated to contribute to hyperglycemia by affecting both α and β-cells of the pancreatic islets of mice. In this report, it was also shown that glucose-stimulated insulin secretion was decreased, whereas glucagon secretion was increased in the islet cells isolated from mice [29]. In a diabetes model created on low-dose streptozotocin and a high-fat/high-fructose diet, it was measured a decreased the islet number, but an increased the islet size at the end of 54-week in rats [30]. Also, it has been demonstrated that high-fat/high-fructose diet increased the density of medium and large-size islets in female rats [31]. Similarly, in another study, a long-term high-fat/high-fructose diet caused to induction of alterations in the islet size and abnormal secretory activities in the pancreas [32]. All the above-mentioned studies indicate that excessive fructose intake may induce morphological changes in the pancreas. The possible mechanisms underlying these alterations are subjected to the following sections. In figure, the potential mechanisms in the pancreas triggered by high-fructose intake are schematized.

4. THE EFFECTS OF HIGH-FRUCTOSE DIET ON CELLULAR STRESS IN PANCREAS

We mentioned above that in the prediabetic state, β-cells increase insulin secretion to compensate the increased blood sugar levels. In this process, the increased intracellular calcium concentration may lead to the induction of reactive oxygen radicals (ROS) and other oxidant molecules such as superoxide, hydrogen

peroxide, and peroxynitrite [33]. On the other hand, oxidative stress caused by glucolipotoxicity, which is a combined effect of high glucose and fatty acids, plays the most decisive role in the onset and worsening of diabetes as well as its complications [34]. In T2D, this oxidative stress generates both apoptotic and destructive changes in pancreatic β-cells [6]. Moreover, high oxidative stress in diabetes can activate nuclear factor kappa-B (NFκB) production and p38 mitogen-activated protein kinase (MAPK) pathway [35, 36]. It is accepted that



the formation of proinflammatory cytokines such as interleukin (IL)1β, IL6, and inducible nitric oxide synthase (iNOS) is triggered by NFκB activation with excessive generation of free oxygen radicals. In the consequence of these events, the destruction of β-cells is accelerated, and thus insulin resistance is worsened [37].

Figure Schematic representation of the potential mechanisms in high-fructose diet-induced β-cell destruction in the pancreas. The arrows show activation. The red arrows indicate the increased (pointing upwards) or decreased (pointing downward) modification.

Moreover, nuclear factor erythroid 2-related factor 2 (Nrf2), one of the cellular defense systems, is activated to manage the oxidative stress. The destruction of β-cells is increased in the situation of insufficient or suppressed cytoprotective factor Nrf2 [38]. In a study conducted in transgenic mice, it was shown that genetic Nrf2 induction preserves the insulin-positive cell area and the integrity of β-cells by suppressing peroxynitrite and hydroxyl radical formation [39]. It was established that a high-fructose diet increased the production of tumor necrosis factor α (TNFα) and malondialdehyde (MDA), as well as leukocyte infiltration into pancreatic tissue [40]. Furthermore, high-fructose corn syrup consumption caused a decrease in catalase (CAT), which is an antioxidant enzyme, but an increase in MDA levels in the pancreatic tissue of female rats [41].

Sirtuin 1 (SIRT1) plays a role in the regulation of glucose-stimulated insulin secretion as well as in the protection of β-cells from oxidative stress [42, 43]. Also, it was found that SIRT1 gene activation in pancreatic

β-cells increases insulin secretion and improves glucose tolerance in transgenic mice [44]. There are a few studies investigating the dietary fructose-induced possible alterations of SIRT1 expression in the pancreas. In this subject, a fructose-rich diet was shown to cause an increase in gene expressions of iNOS, IL1β, and Bax in the islets isolated from the pancreas of mice, but a decrease in that of SIRT1 [45]. Similarly, in both immunohistochemical and western blotting methods, a decrease in SIRT1 protein expressions was determined in fructose fed rats [46]. Indeed, SIRT1 has been shown to inhibit nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), which is one of the primary sources of ROS production [47]. Besides, NOX activity was determined to increase in the pancreatic tissue of rats fed with fructose. In addition, the treatment with a NOX inhibitor prevented a decrease in β-cell volume and islets number induced by dietary fructose [48]. In a sequential study, a long-term high-fat/high-fructose diet was established firstly to activate the production of oxidative stress and then to cause the inflammation [32].

The endoplasmic reticulum (ER) has important roles in protein synthesis and transport, as well as calcium storage in the cell [49]. ER stress, also known as unfolded or misfolded protein response which causes detrimental effects in cells by activating several cellular processes, such as oxidative status, inflammation, and apoptosis [50]. In T2D, it has been demonstrated that ER stress markers increase in the pancreas, and this may contribute to β-cell dysfunction [51]. ER stress markers, such as glucose regulated protein 78 (GRP78), protein kinase like endoplasmic reticulum kinase (PERK), inositol requiring enzyme 1 (IRE1), X box-binding protein1 (XBP1), and C/EBP homologous protein (CHOP) were found to be elevated in the pancreas of high-fat/high-fructose-fed rats [17]. Similarly, the expression of ER stress-related proteins, including IRE1, PERK, and activating transcription factor 6 (ATF6) were increased in the pancreatic tissue of high-fat/high-fructose-fed rats [52]. Also, it was determined an increase in oxidative parameters, including CAT, glutathione (GSH), and MDA as well as ER stress-related proteins such as binding immunoglobulin protein (BIP) and CHOP in the pancreas of rats fed with a high-fat/high-fructose diet from birth to young adulthood [18]. In conclusion, cellular stress factors may play an important role in pancreatic dysfunction of T2D and high-fructose-induced metabolic disorder.

5. THE EFFECTS OF HIGH-FRUCTOSE ON INFLAMMATORY FACTORS IN PANCREAS

Insulin resistance consists of the combination of hyperglycemia, glucose intolerance, and macrophage infiltration into the pancreas in conjunction with low-grade inflammation [53]. In a recent study, islet inflammation in diabetic patients was found to be associated with pancreatic fat infiltration and insulin resistance [26]. Also, experimental studies have shown that cytokine exposure causes β-cell death by increasing iNOS formation [54, 55]. In addition, activation of inflammatory factors such as NFκB and TNFα triggers the onset and acceleration of pancreatitis by causing premature trypsinogen activation in pancreatic acinar cells [56]. Studies indicated that the destruction of β-cells has occurred through the MAPK and c-Jun N-terminal kinase (JNK) pathways activated by cytokines [7, 57]. In experimentally induced pancreatitis, neutrophil infiltration was found to be accompanied by NFκB and MAPK activation [58, 59]. In high-fat/high-sucrose diet fed rats; it has been found that there was a macrophage infiltration into the pancreas as well as an apoptotic changes in β-cells in association with increased tissue TNFα levels [27]. Similarly, high-fructose diet causes an augmentation in inflammatory cytokines in various tissues such as liver, kidney, blood vessels, adipose tissue, and testis of rats [8, 10, 12, 15, 16]. In a study of Sprague-Dawley rats given high-dose (10.5 g/kg/day) fructose, it was shown an increase in inflammatory cell infiltration into the pancreas [60]. The obvious systemic inflammatory state due to high-fructose diet may also affect pancreatic tissue as well as its function.

6. THE EFFECTS OF HIGH-FRUCTOSE DIET ON MITOGENIC PATHWAY IN PANCREAS

MAPKs transduce extracellular stimuli into a range of cellular actions, including gene expression, mitosis, survival, apoptosis, and differentiation. Of the MAPKs, p38 and JNK are activated in response to various cellular stresses such as heat shock proteins, oxidative factors, and cytokines. On the other hand, extracellular signal-regulated kinase (ERK) 1/2 are stimulated in the presence of several growth factors including insulin [61]. In the prediabetic state, activation of the mitogenic signaling pathway may play a role in increasing secretory capacity of pancreatic β-cells to compensate of hyperglycemia. At first, this is efficient in the maintenance of normoglycemia. However, in the latter period, in which the compensation is insufficient, activation of the mitogenic pathway may induce different cellular processes, such as inflammation and apoptosis. Likewise, studies indicate that the destruction of β-cells occurs via the MAPK and JNK pathways activated by cytokines [7]. In a study conducted in streptozotocin-induced diabetic mice, deletion of the MAPK

gene has been shown to prevent leukocyte infiltration and cytokine formation, as well as β-cell destruction [62]. In the diabetes model induced by a high-fat diet and streptozotocin, there was an increase in NFκB, p38 MAPK, and JNK protein expressions but a decrease in Nrf2 in the pancreatic tissue of rats [63]. Also, it was determined that a high-fat/high-fructose diet led to an increase in JNK expression and mononuclear cell infiltration as well as in the destruction of pancreatic islets in rats [17]. Furthermore, in a study, it was demonstrated that pancreatic p38 and JNK expressions were increased in the diabetic group, and treatment of metformin, which is an oral antidiabetic drug, inhibited the activation of these proteins [64]. Mitogenic factors have been shown to play a role in pancreatic dysfunction in diabetes. Excessive fructose intake may also cause destructive effects on the structure and function of the pancreas by causing the activation of mitogenic pathways.

7. THE EFFECTS OF HIGH-FRUCTOSE DIET ON APOPTOSIS IN PANCREAS

Apoptosis, also known as programmed cell death, is a physiological process required for the construction, maintenance, and repair of tissues as well as the destruction of damaged cells. In making the apoptosis decision, many factors are involved, such as p53, Bax, Bcl2, and caspases [65]. In the cytosol and nucleus, p53 involves in the repair of damaged DNA. However, if DNA repair has not occurred, the p53 gene initiates the apoptotic pathway and ensures the elimination of the cell [66]. At the same time, initiator and terminator caspases, which are caspase 8 and caspase 3, and TNFα as well as Fas (CD95) have important functions in the expression of apoptotic cell death signals [67]. It has been shown that suppression of the p53 gene reduces insulin resistance by impairing the activation of inflammatory pathway in the adipose tissue in high-fat/high-sucrose diet-induced diabetes [68]. In a study on diabetic mice, it was suggested that the increase in p53 level may cause apoptosis by stimulating the Fas receptor in pancreatic β-cells [69]. Also, it was shown that a high-fat diet and streptozotocin treatment produce an increase in p53 gene expression and TUNEL-positive cell number in the pancreas [70]. In this line, it was demonstrated that a high-fat/high-fructose diet causes an increase in caspase 3 activity, which is an indicator of apoptosis in the pancreas [17]. Also, it has been shown that high-fat/high-fructose diet increased cleaved-caspase 3 expression in female rats [31]. Notably, the activation of apoptotic factors with high-fructose diet in the pancreatic tissue may trigger structural and functional disturbances in β-cells.

8. CONCLUSION

The current limited studies on excessive fructose consumption suggested that pancreatic disturbances can be initiated by activation of oxidative cellular stress, inflammation, mitogenesis, and apoptosis-related pathways. High-fructose intake may induce morphological changes, including β-cell hyperplasia and hypertrophy in the pancreas at the early period of the disease. In this stage, excess fructose may trigger the activation of mitogenic and apoptotic pathways in the pancreatic tissue. Dietary high-fructose also affects pancreatic function, increasing the secretory activity of β-cell and inducing cellular stress as well as inflammation. Consequently, excessive fructose intake may cause destructive effects on the structure and function of the pancreas. Notably, a better understanding of the mechanisms of pancreatic disturbances observed in the outcomes of high-fructose intake could provide new insights for the prevention and effective treatment of metabolic syndrome. Therefore, it is important to support the above-mentioned initial findings with further studies to create novel potential drug targets. Alternatively, giving up or reducing the consumption of fructose-sweetened beverages and foods would be an efficient approach in the prevention of metabolic diseases more than drug therapy. Because the restriction of dietary fructose, even for a short period (nine days), in obese children has been shown to reduce triglyceride and insulin levels, as well as liver and visceral fat accumulation [71, 72].

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