Dietary Sugars and Diabetes Development from Mitochondrial Perspective

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Type 2 diabetes (T2D) has increased worldwide at an alarming rate. Metabolic syndrome (MetS) is a major risk factor for T2D development. One of the main reasons for the abrupt rise in MetS incidence, besides a sedentary lifestyle, is the westernized diet consumption, with high content of industrialized foods, rich in added dietary sugars (DS), mainly sucrose and fructose. It has been suggested that a higher intake of DS could impair metabolic function, inducing MetS, and predisposing to T2D. However, it remains poorly explored how excessive DS intake modulates mitochondrial function, a key player in metabolism.

Keywords: industrialized food ; dietary sugars ; metabolic dysfunction ; maternal high-sugar diet ; disease programming

1. Introduction

1.1. Metabolic Syndrome Development: The Case of Type 2 Diabetes

The Metabolic Syndrome (MetS) affects around 35% of the adult population in the United States, about 40% in Europe, between 20.7% and 42.7% in the Middle East, and up to 58.1% in >60 age Chinese population [1]. Each region adopts different diagnostic criteria for MetS without general consensus in the medical community [2][3].

The MetS is characterized by a set of metabolic disorders, including dyslipidemia, hypertension, insulin resistance (IR), visceral adipose tissue (VAT) dysfunction, and VAT-related endocrine mediation [3]. Systemic pathophysiological responses are then activated, such as endothelial dysfunction, chronic inflammation, oxidative stress and atherothrombosis [3][4].

Due to the MetS-associated pathophysiology, MetS is one of the major risk factors for type 2 diabetes (T2D) and cardiovascular disease (CVD) development [1][4]. MetS is associated with a 1.36 increased risk of cardiovascular death, 1.46-fold risk of myocardial infarction, 1.43-fold risk of stroke, and 2.92-fold of T2D [5][6].

Distinct components of the MetS have a different impact on T2D development-risk [7]. Among the MetS predisposing factors (e.g., genetic, environmental), diet and sedentary behaviors have been pointed out as the most relevant [3]. The critical role of diet in MetS extends not only to the unbalanced energy intake vs. expenditure but also to the composition of the diets, such as the western diet (WD) which is rich in saturated and unsaturated fats, simple carbohydrates, and poor in fibers, including red meat, processed foods rich in ultra-processed carbohydrates and fats, and re-packaged foods [8].

1.2. The Bitter Risks of Increased Dietary Sugars Consumption

Dietary sugars (DS) correspond to the sugar content of foods that comprehend the sugars naturally present in the food and the sugars added to foods during processing or preparation. Sugars can be labeled as “free sugars” and “intrinsic sugars”. Intrinsic sugars are encapsulated by a cell wall, such as the ones present in brown rice, whole fruit, vegetables, etc. [9]. These tend to be digested at a lower rate and take longer to enter the bloodstream in comparison with “free sugars” [9]. On the contrary, “free sugars” have been refined to some extent, and are not present inside the cells of the food consumed, comprising all the monosaccharides (i.e., glucose, fructose, and galactose) and disaccharides (i.e., sucrose, lactose, and maltose) added to foods by the manufacturer, cook, or consumer, plus sugars present in honey, syrups, and unsweetened fruit juices [9]. Altogether, all naturally-occurring sugars along with the added sugars compose the “total sugars” [10][11].

Sugars can also be referred to as carbohydrates. Carbohydrates encompass the sugars, starches, and dietary fibers that naturally exist in plant-based foods and dairy products, being one of the main energy sources for the human body. During digestion, the carbohydrates are broken down into simple sugars, raising monosaccharides’ blood concentrations. The

carbohydrate's glycemic index (GI) represents the respective increase in blood glucose after the intake of carbohydrates and appears to be critical to define the most concerning classes of sugars. While low GI foods are rich in dietary fibers and induce lower concentrations of fasting triglycerides and LDL-cholesterol, a high intake of elevated GI foods causes IR and contributes to T2D [3].

General consumption of sugars has been rising worldwide over the last decades [12][13]. A primary concern is sugar-sweetened beverages, for which sweeteners are commonly sucrose (composed of glucose and fructose) and corn syrup (rich in fructose) [13]. Fructose overconsumption is a significant driver of MetS development due to its unique metabolization, almost exclusively in the enterocytes and liver, capable of bypassing the hormonal and metabolic regulatory control [13]. Sugar-sweetened beverages and other high energy-dense drinks have a moderate-to-high GI while decreasing satiety and impairing compensatory energy intake [14]. The consumption of these beverages has been associated with T2D development [14].

Nevertheless, the causal relationship between sugar consumption and T2D development has not been scientifically demonstrated. Most of the studies show that the effect of sugars on long-term T2D development is not driven by a direct impact of sugars in the disease pathophysiology, but rather by the promotion of T2D risk factors, such as extra calorie intake, obesity, and MetS that later can lead to IR and T2D phenotype [10]. One possible driver behind this relationship is systemic inflammation which mediators increase due to free-fructose overconsumption [15]. This mechanism, however, seems to be shared by other dietary sugars [16].

Most of the studies point out that, from a sugar-induced disease perspective, the sugar source is not the most important aspect, including sweetened beverages or fruit juices [17][18][19]. Despite more studies being required, mostly related to cellular responses rather than blood parameters and metabolites' landscape, the general literature states that sugar consumption has a modest impact on immediate glycemic control [17][20].

It is important to note that high sugar-containing foods are one of the main sources of energy in infants, children, and adolescents [21], either as a snack or after a regular meal, which contributes to a critically high GI and increased calorie intake, promoting T2D development at early life stages. The hormonal, metabolic, and lifestyle alterations characteristic of adolescence represent a critical period for metabolic disease development, becoming a priority to focus studies on the impact of DS consumption at early ages.

2. The Impact of Dietary Sugars on Mitochondrial Function and Promotion of Type 2 Diabetes

The cellular metabolism of sugars, fats, and amino acids results in chemical energy production in the form of adenosine triphosphate (ATP), mainly by mitochondria [22]. Mitochondria are multifaceted organelles and cellular energy metabolism highly relies on mitochondrial function [22]. Impaired mitochondrial function has been associated with IR mechanisms, ultimately leading to T2D development [23]. In T2D, mitochondrial dysfunction is characterized by decreased electron transport chain (ETC) complexes expression and activity, slower respiration, lower organelle density, decreased ATP maximum synthesis rate, increased reactive oxygen species (ROS) production, and impaired mitochondrial dynamics, with an increased rate of fission events [23]. This has been vastly reported across several organs such as the skeletal muscle, adipose tissue, liver, and heart [23].

2.1. High-Fructose Intake and Mitochondrial Function Modulation

The first step of fructose metabolism requires ATP utilization by the enzyme fructokinase. An exacerbated intake of fructose leads to increasing demand for ATP utilization by the organs [24]. This could be the origin of increased electron flow through the mitochondrial ETC [25]. As insulin-sensitive organs, the liver and the heart are of particular interest to study alterations predisposing to T2D. Studies have proven that in both the livers and hearts of rodent animal models, the intake of an HFr-rich diet leads to the impairment of the mitochondrial ETC complexes' activities and protein content [26][27][28][29], the presence of oxidative stress [30][26][31][27][32], and ultimately, the activation of pro-apoptotic mechanisms [33][34][35][30]. Apoptosis mediated by mitochondria, in both the liver and heart, can lead to tissue inflammation and organ pathologies, ultimately affecting whole-body homeostasis. Altogether, this evidence demonstrates that the overconsumption of fructose, independently of treatment type and duration, can result in mitochondrial dysfunction, impairing cardiac and hepatic mitochondrial respiration, and leading to generating oxidative stress, dysregulating mitochondrial dynamics, and trigger programmed cell death. Nevertheless, the reason behind DS mitochondrial function impairment has not yet been fully disclosed. However, recently, it has been described that mitochondrial dysfunction could

be, in part, induced by an accumulation of dietary advanced glycation end-products (AGEs), due to their elevated presence in processed foods [36][37][38].

3. Type 2 Diabetes and Its Origin in the Womb: The Consequences of Maternal High-Sugar Diet in the Offspring's Metabolic Function

Maternal lifestyle habits, such as the type and quantity of food at preconception [39], gestation [40], and lactation [41], may influence critical periods of fetal/infant development, contributing to future offspring complications [39][40][41][42]. Maternal malnutrition is associated with an increased risk of obesity, T2D, and CVD in young and adult offspring [43][44][45]. Increased generalization of westernized diets, rich in added sugars, even during pregnancy turns vital to study the influence of maternal DS on the offspring's development and health. Although it is well-established that maternal high-processed fat diets programs the offspring to metabolic alterations [46][47], the lack of information concerning appropriate maternal ingestion of added sugars during gestation and/or lactation is evident [48].

While maternal high-DS consumption may be deleterious for the fetus, more human studies are needed to confirm it [49]. Resorting to studies with animal models examining this biological question, it was described that C57BL/6J mice offspring exposed to high-fructose (HFr) during development presented increased: body-weight, blood pressure, glucose area under the curve (AUC), and adipose tissue [47][50]. Sprague-Dawley rat 90-day-old offspring plasma revealed leptinemia, increased IR, and oxidative stress markers (advanced oxidation products (AOPP) and uricemia) in male but not in female offspring [51]. However, 1-year-old C57BL/6J mice female offspring showed increased homeostasis model assessment of insulin resistance (HOMA-IR) score, elevated leptin levels, and decreased adiponectin [47]. Accordingly, 261-day-old Sprague-Dawley rat male offspring exposed to maternal HFr during pregnancy presented similar results [52]. Further analysis in the hepatic tissue showed increased expression of serine phosphorylated form of IRS2, suggesting reduced insulin signaling in the liver [52]. In another study, fetuses of HFr-fed Wistar rats throughout pregnancy until postnatal day-10 showed increased hepatic GLUT5, oppositely to fructokinase mRNA levels, and high triglycerides content [53]. Ten days postnatally, male offspring exhibited decreased expression of hepatic β-oxidation genes, while females showed augmented AMP-activated protein kinase (AMPK) transcript levels in the liver [53]. In fact, phosphorylated AMPKα was decreased in the livers of 22-day-old female offspring of fructose-treated Wistar rats during gestation [54]. Seven-month-old C57BL/6J pups exposed to maternal HFr consumption during pregnancy and lactation presented increased expression of lipogenesis-related proteins and triglycerides accumulation, contributing to altered morphology with increased liver size [50]. This suggests maternal free-HFr-supplemented diet significantly affects liver metabolism and function, predisposing the offspring to obesity, hypertension, and metabolic dysfunction, which are critical risk factors for T2D development. Nevertheless, research to unravel the cellular mechanisms involved is critically necessary.

Few studies explored the effect of maternal fructose consumption on offspring's cardiac tissue. Maternal HFr rodent supplementation resulted in 1-day-old offspring's increased expression of glucose metabolism- and insulin signaling-related genes in the heart and brain, which actively contribute to blood pressure regulation, possibly contributing to the programming of hypertension in adulthood [55]. This period is significant for the offspring's cardiac development since adaptation to the extrauterine life involves a substrate utilization shift from glucose towards fatty acids [56]. Maternal HFr diet during pregnancy and lactation led to mild myocardial hypertrophy in 3-month-old male Sprague-Dawley rat offspring, with collagen fibers deposition and marked oxidative stress in the cardiac tissue [57]. The induced cardiac fibrosis and oxidative damage exacerbated cardiac remodeling [57] for which mitochondria play a crucial role [58].

Concerning the consumption of DS, few studies assessed the effect of maternal diet on the offspring's mitochondrial function. Most focus on brain development and cognitive function. Brain mitochondria of aging Fischer F344 rat offspring exposed to maternal HFr showed decreased P/O_2 ratio [59]. Hippocampi mitochondria of weaned Sprague-Dawley rat offspring after exposure to maternal HFr during pregnancy and lactation showed reduced TFAM mRNA levels and compromised mitochondrial oxygen consumption rates [60]. Studies are lacking to fully understand the role of maternal DS on mitochondrial metabolism and its implications in fetal development and offspring programming of metabolic diseases in adulthood.

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