diabetology

MDPI

Review

The Bitter Side of Sugar Consumption: A Mitochondrial Perspective on Diabetes Development

Mariana S. Diniz [1,2], Carolina Tocantins [1,2], Luís F. Grilo [1,2] and Susana P. Pereira [1,3,*]

[1] CNC—Center for Neuroscience and Cell Biology, CIBB—Centre for Innovative Biomedicine and Biotechnology, University of Coimbra, 3004-531 Coimbra, Portugal
[2] PhD Programme in Experimental Biology and Biomedicine (PDBEB), Institute for Interdisciplinary Research (IIIUC), University of Coimbra, 3004-531 Coimbra, Portugal
[3] Laboratory of Metabolism and Exercise (LaMetEx), Research Centre in Physical Activity, Health and Leisure (CIAFEL), Laboratory for Integrative and Translational Research in Population Health (ITR), Faculty of Sports, University of Porto, 4099-002 Porto, Portugal
* Correspondence: pereirasusan@gmail.com; Tel.: +351-231-249-170

Abstract: 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. This review explores the relationship between increased consumption of DS and mitochondrial dysfunction associated with T2D development, pointing to a contribution of the diet-induced accumulation of advanced glycation end-products (AGEs), with brief insights on the impact of maternal high-sugar diet and AGEs consumption during gestation on offspring increased risk of developing T2D later in life, contributing to perpetuate T2D propagation.

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

Citation: Diniz, M.S.; Tocantins, C.; Grilo, L.F.; Pereira, S.P. The Bitter Side of Sugar Consumption: A Mitochondrial Perspective on Diabetes Development. *Diabetology* **2022**, *3*, 583–595. https://doi.org/10.3390/diabetology3040044

Academic Editor: Peter Clifton

Received: 30 September 2022
Accepted: 1 November 2022
Published: 7 November 2022

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 in 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 [17–19]. 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]. Nevertheless, the impact of DS, namely fructose, on mitochondrial function has been poorly explored. The current section will disclose the current knowledge on the impact of DS in mitochondria across several tissues, especially in the liver and the heart, and how mitochondrial dysfunction induced by excessive ingestion of DS, especially fructose, could prompt T2D development (Figures 1 and 2).

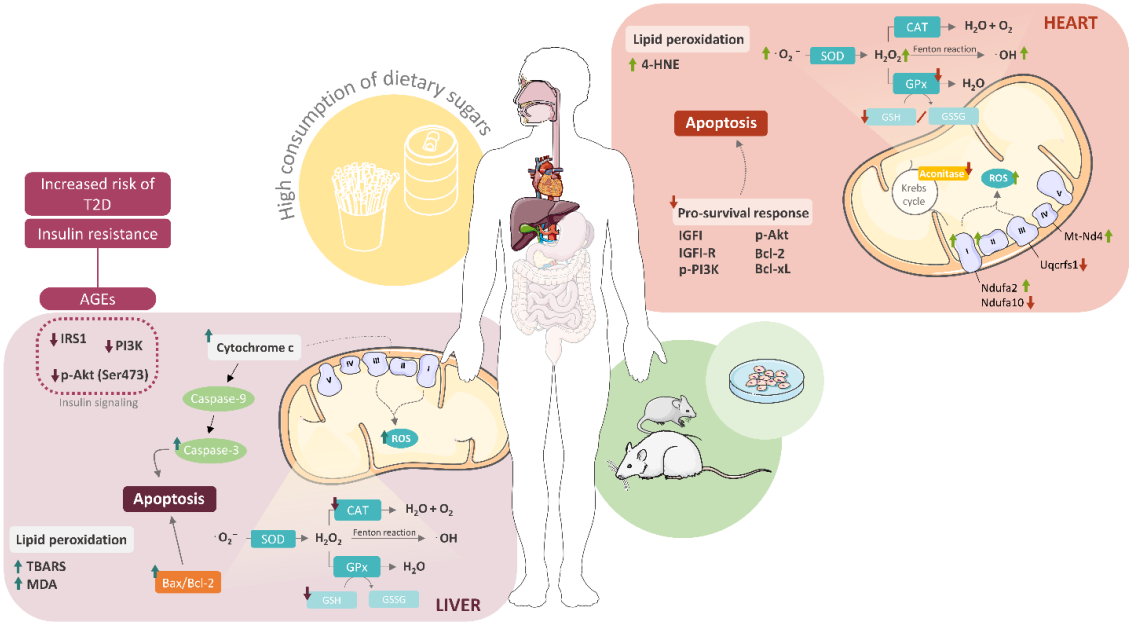

Figure 1. Metabolic alterations induced by high consumption of dietary sugars in the liver and the heart, contributing to mitochondrial dysfunction and the development of risk factors associated with type 2 diabetes (T2D) development. Increased consumption of dietary sugars, especially fructose, leads to impaired mitochondrial respiratory chain function, resulting in altered activity and protein levels of the mitochondrial oxidative phosphorylation system, namely in the subunits of the electron transport chain (I–IV) in the heart. Such alterations contribute to increased reactive oxygen species (ROS) production and inefficient response of the antioxidant defenses. Oxidative stress can induce an apoptotic response by dysregulation of pro-survival and pro-apoptotic proteins. Lipid peroxidation, which contributes to cell damage, is also a result of augmented oxidative stress. Increased levels of advanced glycation end-products (AGEs) interfere with the expression of proteins involved in the insulin signaling pathway, which may promote insulin resistance, a prime risk factor for T2D. IRS1–insulin receptor substrate 1, PI3K-phosphoinositide 3-kinase, Akt–protein kinase B, TBARS-thiobarbituric acid reactive substances, MDA–malondialdehyde, SOD–superoxide dismutase, CAT–catalase, GPx–glutathione peroxidase, 4-HNE-4-Hydroxynonenal, IGFI-insulin-like growth factor 1, IGFI-R–IGFI receptor, GSH–reduced glutathione, GSSG–glutathione disulfide, NDUFA2/10-NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunits 2 and 10, UQCRFS1-ubiquinol-cytochrome *c* reductase iron-sulfur subunit 1, MT-ND4-mitochondrially encoded NADH: ubiquinone oxidoreductase core subunit 4.

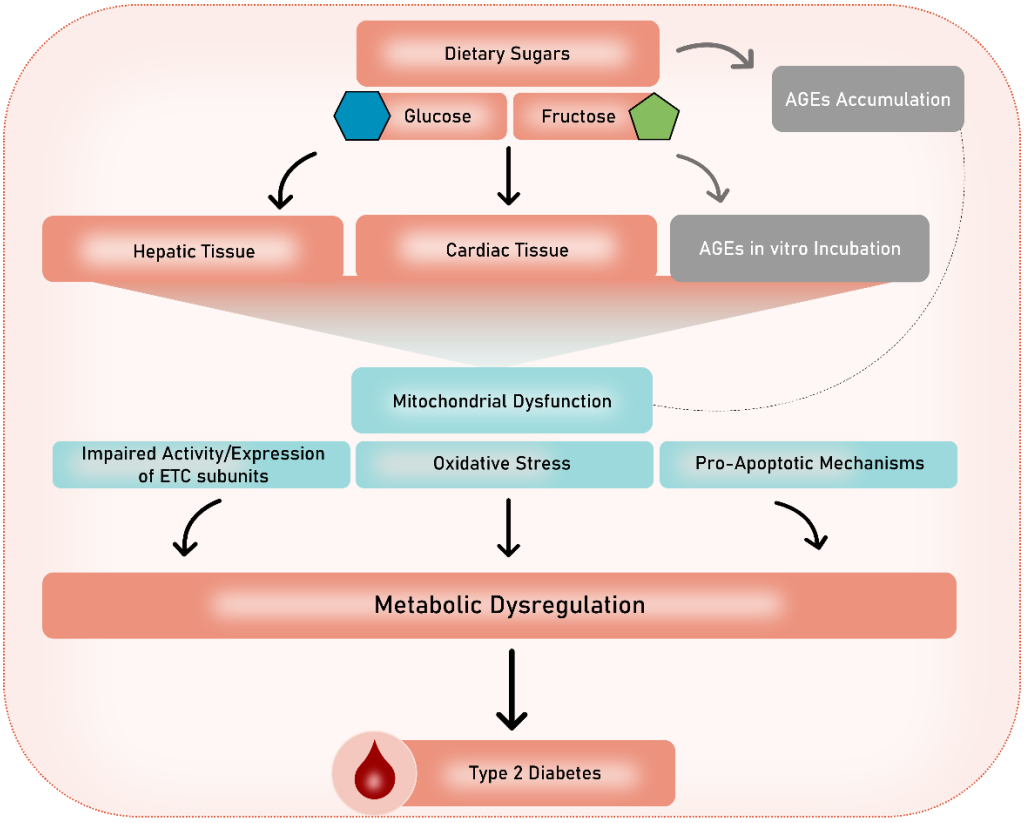

Figure 2. Increased intake of dietary sugars (mainly glucose and fructose) leads to mitochondrial dysfunction. Mitochondrial dysfunction across hepatic and cardiac tissue triggers metabolic dysregulation, including insulin resistance, which ultimately induces the development of type 2 diabetes. In parallel, it is hypothesized that advanced glycation end-products (AGEs) accumulation induced by higher consumption of dietary sugars could lead to mitochondrial dysfunction, through AGEs receptors (RAGEs) activation. Evidence shows that in vitro incubation of different cell lines either with AGEs precursors or AGEs, results in mitochondrial dysfunction, which could act as a starting point to induced metabolic dysregulation and induces type 2 diabetes development.

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 [25,26]. As insulin-sensitive organs, the liver and the heart are of particular interest to study alterations predisposing to T2D. Indeed, in Sprague-Dawley rats, the intake of free high fructose (HFr) for 6 weeks, impairs the activity of mitochondrial ETC, increasing complex-I activity in the heart [27], and 20-week-free HFr treatment decreased complex-II activity in isolated cardiac mitochondria, with decreased mitochondrial oxygen consumption rates and ATP-linked oxygen consumption (state 3–stimulated by the addition of fuel substrates, supports coupled energy conversion) [28,29]. Along with this, proteomic analysis of Wistar rats cardiac tissue after a 24-week HFr-diet identified alterations in the subunits of the ETC, with increased protein content of complex-I, and IV (NDUFA2, Mt-ND4) and decreased complex-I, and III (NDUFA10, UQCRFS1) subunits [29]. In the hepatic tissue, free-HFr treatment for 6 weeks also induced ETC impairment with hepatic mitochondria from free HFr-fed Wistar rats presenting decreased ATP-linked oxygen consumption [30]. HFr diet induced-dysfunctional mitochondrial ETC, with impaired respiration, could induce increased electron escaping through the ETC complexes-I and III, prompting altered mitochondrial membrane potential along with increased electron reactivity with oxygen, leading to an overproduction of ROS, which ultimately could produce biomolecules' oxidative damage. Indeed, evidence of redox imbalance has been reported

in the hepatic and cardiac tissues of HFr-fed murine animal models, independently of the duration and type of HFr treatment. In the liver and heart of dietary HFr/free-HFr fed-rats, lipid peroxidation is increased, demonstrated by increased levels of thiobarbituric acid (TBARS) [31,32], malondialdehyde (MDA) [33], and 4-Hydroxynonenal (4-HNE) [27,32]. In other respects, hepatic antioxidant defenses are diminished, as indicated by decreased superoxide dismutase (SOD) [32] and GSH-S transferase activities [33], lower protein levels of glutathione peroxidase 1 (GPx1) [27], reduced GSH/GSSG ratio [27,28], and diminished catalase activity [34]. In addition, increased production of ROS, assessed through increased superoxide and hydroxyl radicals [28], augmented hydrogen peroxide production [28], and decreased aconitase activity were verified in hepatic and cardiac tissues from HFr-fed rats [27].

Pro-apoptotic mechanisms can be activated by increased oxidative injury [35]. High fructose-induced alterations of proteins involved in cell apoptosis and survival, which are mediated by cell signaling cascades, have been mightily documented in the hearts and livers of HFr-fed murine animal models. An increased number of apoptotic cells has been reported in the cardiac tissue of HFr-fed Wistar rats [36], hepatic tissue of mice [35], and in cardiomyocytes differentiated from an H9C2 rat-myoblastic cell line [37] through the TUNEL assay or DNA strand break labeling, along with increased levels of the activated form of caspase-3 [34], Bax and increased Bax/BcL-2 ratio [33] and cytosolic cytochrome *c* amount [33]. All of these mechanisms are critically involved in the intrinsic mitochondrial apoptotic pathway [31]. Consistently, reports described HFr-induced suppression of pro-survival mechanisms–so-called due to its ability to negatively regulate pro-apoptotic mechanisms, by suppressing the activation of caspases and pro-apoptotic proteins, as confirmed by decreased activation of PI3K and Akt and/or expression levels of the pro-survival proteins, IGFI, IGFI-R, Bcl-2, and Bcl-xL in the cardiac tissues of HFr-fed Wistar rats [36]. Moreover, during the process of apoptosis, it has been reported that mitochondrial dynamics machinery disintegrates for cytochrome *c* release. Mitochondrial kinetics comprehend motility, fusion, fission, biogenesis, and mitophagy. The equilibrium between these processes allows the preservation of mitochondrial number, and morphology and impacts mitochondrial function. Mitochondrial fusion consists of the merging of two adjacent mitochondria. This process can be used, up to a certain level, to alleviate stress by combining the content of partially damaged mitochondria. Mitochondrial fusion is coordinated by proteins that bind and promote membrane fusion, including mitofusin (MFN)- 1 and 2 [38,39]. On the contrary, mitochondrial fission is the mechanism that generates mitochondrial fragmentation; it is driven by proteins that first direct the constriction of membranes and then mitochondrial splitting, including mitochondrial fission factor (MFF), a tail-anchored protein of the mitochondrial outer membrane that acts as the receptor for dynamin-related protein-1 (DRP1), a cytosolic GTPase that tends to oligomerize. The mitochondrial fission protein 1 (FIS1) has been also implicated in mitochondrial fission [38,39]. This process is essential for mitochondrial duplication, but also for the clearance of damaged mitochondria during high levels of cellular stress [38,39]. Thus, maintaining a balance between fission and fusion events is essential to sustain mitochondrial integrity and homeostasis. Several proteins involved in mitochondrial fission and fusion events have been pointed out to act as apoptosis inductors, especially DRP1, which is involved in cytochrome *c* release, FIS1, which is involved in Bax translocation, and optic atrophy 1 (OPA1), which, conversely, prevents mitochondrial fission, protecting cells from apoptosis [40]. It has been shown that primary cell lines treated with glucose, one of the main dietary sugars, exhibit increased mitochondrial fragmentation, which has been suggested to be mediated by hyperglycemia-induced modulation of fission and fusion proteins [41]. Indeed, human umbilical vein-derived endothelial cells (HUVECs) treated with high glucose levels present signs of mitochondrial fragmentation [42]. Cells from the cardiovascular system (i.e., neonatal rat ventricular myocytes, H9C2 cell line, bovine aortic endothelial cells, and mouse aortic smooth muscle cells) treated in hyperglycemic conditions present increased mitochondrial fragmentation, which is induced by an increased expression of the protein DRP1/DLP1,

mediating hyperglycemia-induced cell death [41]. Moreover, proximal tubular cell lines (HK-2), present increased mitochondrial fragmentation induced by hyperglycemic conditions, which is preserved by the pharmacological modulation of proteins involved in mitochondrial dynamics (FIS1, DRP1, MFN1, and MFN2) [43]. These findings reflect a potential deleterious effect of dietary sugars on mitochondrial dynamics that, ultimately, could cause cell death. Nevertheless, more studies are required to deepen this potential impairment and compare it to fructose-treated cell lines, along with the complementation of data from animal models treated with high-glucose/fructose diets.

Apoptosis mediated by mitochondria, in both the liver and heart, can lead to tissue inflammation and organ pathologies, ultimately affecting whole-body homeostasis. Altogether, the evidence discussed above demonstrates that the overconsumption of fructose, independently of treatment type and duration, can result in mitochondrial dysfunction, impairing cardiac and hepatic mitochondrial respiration, 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 [44,45].

2.2. Advanced Glycation End-Products Accumulation Induce Mitochondrial Dysfunction: A Potential Mechanism in Type 2 Diabetes

Advanced glycation end-products have been pointed out as potential biomarkers of a diabetic condition, inducing IR and, possibly, mitochondrial dysfunction [46]. AGEs are the result of the "Maillard reaction" [47], which is described as a non-enzymatic spontaneous reaction between reducing sugars with lipids, nucleic acids, and free amino acid groups from proteins [47]. In addition, AGEs can also be a product of the oxidation of sugars, lipids, and amino acids [48]. However, reducing sugars are one of the main sources of AGEs [47]. Interestingly, in vitro observations have indicated that fructose is one of the most potent glycation agents [49]. Hyperglycemia could prompt AGEs accumulation, which could play a major pathologic role in contributing to the dysregulation of many cellular functions in the organism [50], predisposing to the development of T2D. Indeed, AGEs are toxic metabolic byproducts, and the effects of AGEs' whole-body accumulation have been documented in diverse mechanisms (i.e., de novo lipid synthesis, lipogenic pathway, inflammatory response) [49]. Specifically, the development of IR has been associated with systemic AGEs accumulation in mouse animal models and even in humans [51]. On the other hand, AGEs restriction prevents IR, highlighting the role of AGEs in the development of IR-related mechanisms [46]. Although the specific mechanisms by which AGEs induce IR remain unknown, dietary-AGEs impaired insulin signaling pathway has been verified in both in vitro and in vivo models [51]. Hepatocytes, adipocytes, and pancreatic beta cells treated with AGEs precursor [51], methylglyoxal (MG), which is a metabolite of the glycolytic pathway, show decreased activation of insulin receptor substrate 1 (IRS1), Akt phosphorylation in the Ser473 residue [51], and reduced activity of phosphoinositide 3-kinase (PI3K) [52]. Additionally, Sprague-Dawley rats with a 4-week administration of MG presented enhanced insulin resistance, which was evaluated through the euglycemic hyperinsulinemic glucose clamp technique in the circulating blood [53]. The overproduction of AGEs could also contribute to the activation of membrane receptors, such as RAGEs [26], inducing a cycle of mitochondrial dysfunction and oxidative damage, and promoting apoptosis [54]. Evidence suggests that RAGEs activation could stimulate complex-I, leading to increased ROS production, prompting the organism for oxidative stress [54]. In spite of this, decreased activities of complex-I and -IV were verified in the cerebral cortex of mice fed with a MG-rich diet [55] and in human retinal pigmented epithelium cell lines treated with AGE-BSA [56]. Nevertheless, the presence of oxidative stress is confirmed in most studies, describing increased production of superoxide anion, or hydrogen peroxide, and/or loss of MnSOD activity in the serum of MG-fed mice [55], beta cells [57], endothelial

progenitor cells [54], and chondrogenic cells [56] treated with AGEs (N^{ε}-carboxymethyl lysine (CML), when mentioned [57]). Furthermore, AGEs treatment appeared to induce ATP depletion in MG-treated adipocytes [55], loss of mitochondrial membrane potential, and apoptosis, which is confirmed through increased Bax/BcL-2 ratio and increased release of cleaved caspase 3 in AGEs-treated chondrogenic ATDC5 cells [56]. Even though this has been mostly documented for in vitro models, data concerning in vivo and tissue-targeted studies is still lacking and demands further investigation so the relationship between AGEs accumulation, IR, and mitochondrial dysfunction can be established and ultimately, fully understand the contribution of AGEs accumulation and mechanism for inducing T2D development potentiating new preventative strategies for T2D development.

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 [58], gestation [59], and lactation [60], may influence critical periods of fetal/infant development, contributing to future offspring complications [58–61]. Maternal malnutrition is associated with an increased risk of obesity, T2D, and CVD in young and adult offspring [62–64]. 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 [65,66], the lack of information concerning appropriate maternal ingestion of added sugars during gestation and/or lactation is evident [67].

While maternal high-DS consumption may be deleterious for the fetus, more human studies are needed to confirm it [68]. Resorting to studies with animal models examining this biological question, it was described that C57BL/6J mice offspring exposed to HFr during development presented increased: body-weight, blood pressure, glucose area under the curve (AUC), and adipose tissue [66,69]. 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 [70]. 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 [66]. Accordingly, 261-day-old Sprague-Dawley rat male offspring exposed to maternal HFr during pregnancy presented similar results [71]. Further analysis in the hepatic tissue showed increased expression of serine phosphorylated form of IRS2, suggesting reduced insulin signaling in the liver [71]. 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 [72]. 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 [72]. In fact, phosphorylated AMPKα was decreased in the livers of 22-day-old female offspring of fructose-treated Wistar rats during gestation [73]. 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 [69]. 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 [74]. 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 [75]. 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 [76]. The induced cardiac fibrosis and oxidative damage exacerbated cardiac remodeling [76] for which mitochondria play a crucial role [77].

Another characteristic of WD is the concomitant high intake of AGEs. Serum AGEs (sAGEs) have been proposed to be maternally transferred through the placenta [78]. Nonetheless, the levels of sAGEs might reflect dietary AGEs consumption [79]. Young-adult offspring of C57BL/6 mice from mothers fed an AGEs-rich diet (with increased CML content) showed reduced insulin sensitivity and increased body weight [80]. As briefly mentioned, maternal diet during lactation may also affect perinatal development since it influences breast milk composition [81]. Offspring of MG-treated Wistar rat mothers developed increased body weight, adipose tissue, glucose intolerance, and β-cell dysfunction in adulthood, increasing their predisposition for T2D [81].

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 [82]. 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 [83]. 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.

4. Mitochondrial-Targeted Therapies for T2D Management

The clinically well-established treatment of T2D with metformin presents the capacity of shifting the main energy substrate used across several tissues [23], the ability to modulate mitochondrial dynamics, especially mitochondrial fission events in endothelial cells, and prevent superoxide generation [23]. In addition, metformin has been suggested to inhibit mitochondrial complex-I activity, which is an extremely relevant feature from a therapeutic perspective [84].

Dietary supplementation has been also demonstrated to have positive effects in modulating mitochondrial function. For example, flavonoids from mulberry leaves have been suggested to improve skeletal muscle mitochondrial function in diabetic mice, through the modulation of the AMPK/peroxisome proliferator-activated receptor- γ coactivator 1 α axis (AMPK/PGC-1α) [85], highlighting a potential role in T2D management [85]. Other studies have suggested that by inhibiting fructose metabolism through ketohexokinase [86], the primary fructose metabolizing enzyme, and fructose-1,6-bisphosphatase [87], it could be possible to prevent the development of metabolic disease, including T2D. Both approaches seem to prevent hyperinsulinemia and hyperglycemia, thus highlighting novel therapeutic approaches to T2D. It is though relevant to mention that more straightforward approaches have been suggested, such as the removal of fructose from the diet [88]. Indeed, diet-switching reversed mitochondrial function and prevented oxidative stress in the hippocampus of Wistar rats [88]. More studies across other tissues are required to understand if mitochondrial function improvement is verified as well. Nonetheless, given that, in theory, this is a relatively simple strategy to be implemented it is highly relevant for T2D clinical management, making it worth the additional efforts to overcome the challenges of adherence to nutritional interventions, particularly during pregnancy. Given maternal HFr-induced deleterious effects on the offspring's metabolism across many tissues (Section 3), it is also worth mentioning that a study revealed that the administration of Coenzyme Q10 in the offspring, which is a key-mediator of mitochondrial ETC [89], improved mitochondrial biogenesis, and ATP levels, preventing maternal HFr-diet-induced adverse effects in the retinas of female offspring [89].

Mitochondrial-based therapies have a great potential to be explored in T2D prevention and treatment. The follow-up of these studies or new studies could give origin to improved strategies to counteract T2D, even before birth, thus reducing the global burden of this metabolic disease.

5. Conclusions

The overconsumption of free sugars significantly contributes to whole-body DS excess and could severely impact mitochondrial function through alterations in the subunits' expression levels and in the enzymatic activity of the ETC complexes, leading to oxidative stress, mitochondrial dynamics impairment, and activation of apoptotic mechanisms. DS-induced mitochondrial dysfunction can be a result of an accumulation of dietary AGEs, nevertheless, further studies are demanded to confirm this hypothesis and to establish a solid relationship between excessive DS consumption and T2D development. In addition, maternal high-sugar diet consumption impacts the offspring's metabolism at different time-points in the lifetime (i.e., fetal, neonatal, and postnatal stages), in a sex-dependent way, across different animal models, and along with increased levels of AGEs, could predispose the offspring for T2D development.

Author Contributions: All the authors have responsibility for the entire content of this manuscript and approve its submission. Conceptualization, M.S.D., C.T., L.F.G. and S.P.P.; investigation, M.S.D., C.T., L.F.G. and S.P.P.; resources, M.S.D., C.T., L.F.G. and S.P.P.; visualization, M.S.D. and C.T. writing—original draft, M.S.D., C.T. and L.F.G.; writing—review and editing, M.S.D., C.T., L.F.G. and S.P.P.; supervision—S.P.P.; project administration S.P.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the ERDF funds through the Operational Programme for Competitiveness–COMPETE 2020 and national funds by Foundation for Science and Technology under FCT-Post-doctoral Fellowship (SPP, SFRH/BPD/116061/2016), FCT-doctoral Fellowship (MSD, SFRH/BD/11934/2022; CT, SFRH/BD/11924/2022; LFG, SFRH/BD/5539/2020), project grant PTDC/DTP-DES/1082/2014 (POCI-01-0145-FEDER-016657), CENTRO-01-0246-FEDER-000010 (Multidisciplinary Institute of Ageing in Coimbra), strategic projects UIDB/04539/2020, UIDP/04539/2020, and LA/P/0058/2020, Fulbright Scholarship for Research (LFG), and Luso-American Development Foundation, R&D at USA Grant (LFG).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. McCracken, E.; Monaghan, M.; Sreenivasan, S. Pathophysiology of the Metabolic Syndrome. *Clin. Dermatol.* **2018**, *36*, 14–20. [CrossRef]
2. Lemieux, I.; Després, J.P. Metabolic Syndrome: Past, Present and Future. *Nutrients* **2020**, *12*, 3501. [CrossRef] [PubMed]
3. Bovolini, A.; Garcia, J.; Andrade, M.A.; Duarte, J.A. Metabolic Syndrome Pathophysiology and Predisposing Factors. *Int. J. Sports Med.* **2021**, *42*, 199–214. [CrossRef]
4. Gonzalez-Chávez, A.; Chávez-Fernández, J.A.; Elizondo-Argueta, S.; González-Tapia, A.; León-Pedroza, J.I.; Ochoa, C. Metabolic Syndrome and Cardiovascular Disease: A Health Challenge. *Arch. Med. Res.* **2018**, *49*, 516–521. [CrossRef] [PubMed]
5. Lee, Y.-B.; Kim, D.H.; Kim, S.M.; Kim, N.H.; Choi, K.M.; Baik, S.H.; Park, Y.G.; Han, K.; Yoo, H.J. Risk of Type 2 Diabetes According to the Cumulative Exposure to Metabolic Syndrome or Obesity: A Nationwide Population-based Study. *J. Diabetes Investig.* **2020**, *11*, 1583. [CrossRef]
6. Li, X.; Zhai, Y.; Zhao, J.; He, H.; Li, Y.; Liu, Y.; Feng, A.; Li, L.; Huang, T.; Xu, A.; et al. Impact of Metabolic Syndrome and It's Components on Prognosis in Patients with Cardiovascular Diseases: A Meta-Analysis. *Front. Cardiovasc. Med.* **2021**, *8*, 704145. [CrossRef]
7. Marott, S.C.W.; Nordestgaard, B.G.; Tybjærg-Hansen, A.; Benn, M. Components of the Metabolic Syndrome and Risk of Type 2 Diabetes. *J. Clin. Endocrinol. Metab.* **2016**, *101*, 3212–3221. [CrossRef]

8. Rodríguez-Monforte, M.; Sánchez, E.; Barrio, F.; Costa, B.; Flores-Mateo, G. Metabolic Syndrome and Dietary Patterns: A Systematic Review and Meta-Analysis of Observational Studies. *Eur. J. Nutr.* **2017**, *56*, 925–947. [CrossRef]
9. Redruello-Requejo, M.; Samaniego-Vaesken, M.D.L.; Partearroyo, T.; Rodríguez-Alonso, P.; Soto-Méndez, M.J.; Hernández-Ruiz, Á.; Villoslada, F.L.; Leis, R.; de Victoria, E.M.; Moreno, J.M.; et al. Dietary Intake of Individual (Intrinsic and Added) Sugars and Food Sources from Spanish Children Aged One to <10 Years-Results from the EsNuPI Study. *Nutrients* **2022**, *14*, 1667. [CrossRef]
10. Prinz, P. The Role of Dietary Sugars in Health: Molecular Composition or Just Calories? *Eur. J. Clin. Nutr.* **2019**, *73*, 1216–1223. [CrossRef]
11. Fidler Mis, N.; Braegger, C.; Bronsky, J.; Campoy, C.; Domellöf, M.; Embleton, N.D.; Hojsak, I.; Hulst, J.; Indrio, F.; Lapillonne, A.; et al. Sugar in Infants, Children and Adolescents: A Position Paper of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J. Pediatr. Gastroenterol. Nutr.* **2017**, *65*, 681–696. [CrossRef]
12. Newens, K.J.; Walton, J. A Review of Sugar Consumption from Nationally Representative Dietary Surveys across the World. *J. Hum. Nutr. Diet.* **2016**, *29*, 225–240. [CrossRef] [PubMed]
13. Taskinen, M.R.; Packard, C.J.; Borén, J. Dietary Fructose and the Metabolic Syndrome. *Nutrients* **2019**, *11*, 1987. [CrossRef] [PubMed]
14. Malik, V.S.; Hu, F.B. Sugar-Sweetened Beverages and Cardiometabolic Health: An Update of the Evidence. *Nutrients* **2019**, *11*, 1840. [CrossRef] [PubMed]
15. Cox, C.L.; Stanhope, K.L.; Schwarz, J.M.; Graham, J.L.; Hatcher, B.; Griffen, S.C.; Bremer, A.A.; Berglund, L.; McGahan, J.P.; Keim, N.L.; et al. Circulating Concentrations of Monocyte Chemoattractant Protein-1, Plasminogen Activator Inhibitor-1, and Soluble Leukocyte Adhesion Molecule-1 in Overweight/Obese Men and Women Consuming Fructose- or Glucose-Sweetened Beverages for 10 Weeks. *J. Clin. Endocrinol. Metab.* **2011**, *96*, E2034–E2038. [CrossRef]
16. Della Corte, K.W.; Perrar, I.; Penczynski, K.J.; Schwingshackl, L.; Herder, C.; Buyken, A.E. Effect of Dietary Sugar Intake on Biomarkers of Subclinical Inflammation: A Systematic Review and Meta-Analysis of Intervention Studies. *Nutrients* **2018**, *10*, 606. [CrossRef]
17. Della Corte, K.A.; Penczynski, K.; Kuhnle, G.; Perrar, I.; Herder, C.; Roden, M.; Wudy, S.A.; Remer, T.; Alexy, U.; Buyken, A.E. The Prospective Association of Dietary Sugar Intake in Adolescence with Risk Markers of Type 2 Diabetes in Young Adulthood. *Front. Nutr.* **2021**, *7*, 362. [CrossRef]
18. Gill, J.M.R.; Sattar, N. Fruit Juice: Just Another Sugary Drink? *Lancet Diabetes Endocrinol.* **2014**, *2*, 444–446. [CrossRef]
19. Imamura, F.; O'Connor, L.; Ye, Z.; Mursu, J.; Hayashino, Y.; Bhupathiraju, S.N.; Forouhi, N.G. Consumption of Sugar Sweetened Beverages, Artificially Sweetened Beverages, and Fruit Juice and Incidence of Type 2 Diabetes: Systematic Review, Meta-Analysis, and Estimation of Population Attributable Fraction. *BMJ* **2015**, *351*, h3576. [CrossRef]
20. Choo, V.L.; Viguiliouk, E.; Blanco Mejia, S.; Cozma, A.I.; Khan, T.A.; Ha, V.; Wolever, T.M.S.; Leiter, L.A.; Vuksan, V.; Kendall, C.W.C.; et al. Food Sources of Fructose-Containing Sugars and Glycaemic Control: Systematic Review and Meta-Analysis of Controlled Intervention Studies. *BMJ* **2018**, *363*, k4644. [CrossRef]
21. Paglia, L. The Sweet Danger of Added Sugars. *Eur. J. Paediatr. Dent.* **2019**, *20*, 89. [CrossRef] [PubMed]
22. Spinelli, J.B.; Haigis, M.C. The Multifaceted Contributions of Mitochondria to Cellular Metabolism. *Nat. Cell Biol.* **2018**, *20*, 745. [CrossRef] [PubMed]
23. Pinti, M.v.; Fink, G.K.; Hathaway, Q.A.; Durr, A.J.; Kunovac, A.; Hollander, J.M.; Mv, P.; Gk, F.; Qa, H.; Aj, D.; et al. Mitochondrial dysfunction in type 2 diabetes mellitus: An organ-based analysis. *J. Physiol. Endocrinol. Metab.* **2019**, *316*, 268–285. [CrossRef] [PubMed]
24. Abdelmalek, M.F.; Suzuki, A.; Guy, C.; Unalp-Arida, A.; Colvin, R.; Johnson, R.J.; Diehl, A.M. Increased Fructose Consumption Is Associated with Fibrosis Severity in Patients with Nonalcoholic Fatty Liver Disease. *Hepatology* **2010**, *51*, 1961–1971. [CrossRef] [PubMed]
25. Sil, R.; Chakraborti, A.S. Oxidative Inactivation of Liver Mitochondria in High Fructose Diet-Induced Metabolic Syndrome in Rats: Effect of Glycyrrhizin Treatment. *Phytother. Res.* **2016**, *30*, 1503–1512. [CrossRef]
26. Grilo, L.F.; Tocantins, C.; Diniz, M.S.; Gomes, R.M.; Oliveira, P.J.; Matafome, P.; Pereira, S.P. Metabolic Disease Programming: From Mitochondria to Epigenetics, Glucocorticoid Signalling and Beyond. *Eur. J. Clin. Investig.* **2021**, *51*, e13625. [CrossRef]
27. Lou, P.H.; Lucchinetti, E.; Scott, K.Y.; Huang, Y.; Gandhi, M.; Hersberger, M.; Clanachan, A.S.; Lemieux, H.; Zaugg, M. Alterations in Fatty Acid Metabolism and Sirtuin Signaling Characterize Early Type-2 Diabetic Hearts of Fructose-Fed Rats. *Physiol. Rep.* **2017**, *5*, e13388. [CrossRef]
28. Zhang, Y.B.; Meng, Y.H.; Chang, S.; Zhang, R.Y.; Shi, C. High Fructose Causes Cardiac Hypertrophy via Mitochondrial Signaling Pathway. *Am. J. Transl. Res.* **2016**, *8*, 4869.
29. Szűcs, G.; Sója, A.; Péter, M.; Sárközy, M.; Bruszel, B.; Siska, A.; Földesi, I.; Szabó, Z.; Janáky, T.; Vígh, L.; et al. Prediabetes Induced by Fructose-Enriched Diet Influences Cardiac Lipidome and Proteome and Leads to Deterioration of Cardiac Function Prior to the Development of Excessive Oxidative Stress and Cell Damage. *Oxidative Med. Cell. Longev.* **2019**, *2019*, 3218275. [CrossRef]
30. García-Berumen, C.I.; Ortiz-Avila, O.; Vargas-Vargas, M.A.; del Rosario-Tamayo, B.A.; Guajardo-López, C.; Saavedra-Molina, A.; Rodríguez-Orozco, A.R.; Cortés-Rojo, C. The Severity of Rat Liver Injury by Fructose and High Fat Depends on the Degree of Respiratory Dysfunction and Oxidative Stress Induced in Mitochondria. *Lipids Health Dis.* **2019**, *18*, 78. [CrossRef]
31. Cioffi, F.; Senese, R.; Lasala, P.; Ziello, A.; Mazzoli, A.; Crescenzo, R.; Liverini, G.; Lanni, A.; Goglia, F.; Iossa, S. Fructose-Rich Diet Affects Mitochondrial DNA Damage and Repair in Rats. *Nutrients* **2017**, *9*, 323. [CrossRef] [PubMed]

32. Kannappan, S.; Palanisamy, N.; Anuradha, C.V. Suppression of Hepatic Oxidative Events and Regulation of ENOS Expression in the Liver by Naringenin in Fructose-Administered Rats. *Eur. J. Pharmacol.* **2010**, *645*, 177–184. [CrossRef] [PubMed]
33. Zaki, S.M.; Fattah, S.A.; Hassan, D.S. The Differential Effects of High-Fat and High-Fructose Diets on the Liver of Male Albino Rat and the Proposed Underlying Mechanisms. *Folia Morphol. (Warsz)* **2019**, *78*, 124–136. [CrossRef] [PubMed]
34. Beydogan, A.B.; Coskun, Z.M.; Bolkent, S. The Protective Effects of Δ9-Tetrahydrocannabinol against Inflammation and Oxidative Stress in Rat Liver with Fructose-Induced Hyperinsulinemia. *J. Pharm. Pharmacol.* **2019**, *71*, 408–416. [CrossRef] [PubMed]
35. Choi, Y.; Abdelmegeed, M.A.; Song, B.J. Diet High in Fructose Promotes Liver Steatosis and Hepatocyte Apoptosis in C57BL/6J Female Mice: Role of Disturbed Lipid Homeostasis and Increased Oxidative Stress. *Food Chem. Toxicol.* **2017**, *103*, 111–121. [CrossRef]
36. Cheng, S.M.; Cheng, Y.J.; Wu, L.Y.; Kuo, C.H.; Lee, Y.S.; Wu, M.C.; Huang, C.Y.; Ting, H.; Lee, S.-D. Activated Apoptotic and Anti-Survival Effects on Rat Hearts with Fructose Induced Metabolic Syndrome. *Cell Biochem. Funct.* **2014**, *32*, 133–141. [CrossRef]
37. Park, J.H.; Ku, H.J.; Kim, J.K.; Park, J.-W.; Lee, J.H. Amelioration of High Fructose-Induced Cardiac Hypertrophy by Naringin. *Sci. Rep.* **2018**, *8*, 9464. [CrossRef]
38. Kornfeld, O.S.; Qvit, N.; Haileselassie, B.; Shamloo, M.; Bernardi, P.; Mochly-Rosen, D. Interaction of Mitochondrial Fission Factor with Dynamin Related Protein 1 Governs Physiological Mitochondrial Function In Vivo. *Sci. Rep.* **2018**, *8*, 14034. [CrossRef]
39. Ihenacho, U.K.; Meacham, K.A.; Harwig, M.C.; Widlansky, M.E.; Hill, R.B. Mitochondrial Fission Protein 1: Emerging Roles in Organellar Form and Function in Health and Disease. *Front. Endocrinol. (Lausanne)* **2021**, *12*, 274. [CrossRef]
40. Suen, D.F.; Norris, K.L.; Youle, R.J. Mitochondrial Dynamics and Apoptosis. *Genes Dev.* **2008**, *22*, 1577–1590. [CrossRef]
41. Yu, T.; Sheu, S.S.; Robotham, J.L.; Yoon, Y. Mitochondrial Fission Mediates High Glucose-Induced Cell Death through Elevated Production of Reactive Oxygen Species. *Cardiovasc. Res.* **2008**, *79*, 341–351. [CrossRef] [PubMed]
42. Zheng, Y.; Luo, A.; Liu, X. The Imbalance of Mitochondrial Fusion/Fission Drives High-Glucose-Induced Vascular Injury. *Biomolecules* **2021**, *11*, 1779. [CrossRef] [PubMed]
43. Lee, W.C.; Chau, Y.Y.; Ng, H.Y.; Chen, C.H.; Wang, P.W.; Liou, C.W.; Lin, T.K.; Chen, J.B. Empagliflozin Protects HK-2 Cells from High Glucose-Mediated Injuries via a Mitochondrial Mechanism. *Cells* **2019**, *8*, 1085. [CrossRef]
44. Wang, X.; Yu, S.; Wang, C.Y.; Wang, Y.; Liu, H.X.; Cui, Y.; Zhang, L.-D. Advanced Glycation End Products Induce Oxidative Stress and Mitochondrial Dysfunction in SH-SY5Y Cells. *Vitr. Cell. Dev. Biol.-Anim.* **2015**, *51*, 204–209. [CrossRef] [PubMed]
45. Sung, S.K.; Woo, J.S.; Kim, Y.H.; Son, D.W.; Lee, S.W.; Song, G.S. Sildenafil Ameliorates Advanced Glycation End Products-Induced Mitochondrial Dysfunction in HT-22 Hippocampal Neuronal Cells. *J. Korean Neurosurg. Soc.* **2016**, *59*, 259–268. [CrossRef]
46. Ottum, M.S.; Mistry, A.M. Advanced Glycation End-Products: Modifiable Environmental Factors Profoundly Mediate Insulin Resistance. *J. Clin. Biochem. Nutr.* **2015**, *57*, 1–12. [CrossRef] [PubMed]
47. Singh, R.; Barden, A.; Mori, T.; Beilin, L. Advanced Glycation End-Products: A Review. *Diabetologia* **2001**, *44*, 129–146. [CrossRef]
48. Uribarri, J.; del Castillo, M.D.; de la Maza, M.P.; Filip, R.; Gugliucci, A.; Luevano-Contreras, C.; Macías-Cervantes, M.H.; Markowicz Bastos, D.H.; Medrano, A.; Menini, T.; et al. Dietary Advanced Glycation End Products and Their Role in Health and Disease. *Adv. Nutr.* **2015**, *6*, 461–473. [CrossRef]
49. Aragno, M.; Mastrocola, R. Dietary Sugars and Endogenous Formation of Advanced Glycation Endproducts: Emerging Mechanisms of Disease. *Nutrients* **2017**, *9*, 385. [CrossRef]
50. Yamagishi, S.; Matsui, T. Pathologic Role of Dietary Advanced Glycation End Products in Cardiometabolic Disorders, and Therapeutic Intervention. *Nutrition* **2016**, *32*, 157–165. [CrossRef]
51. Ruiz, H.H.; Ramasamy, R.; Schmidt, A.M. Advanced Glycation End Products: Building on the Concept of the "Common Soil" in Metabolic Disease. *Endocrinology* **2020**, *161*, bqz006. [CrossRef] [PubMed]
52. Jia, X.; Wu, L. Accumulation of Endogenous Methylglyoxal Impaired Insulin Signaling in Adipose Tissue of Fructose-Fed Rats. *Mol. Cell. Biochem.* **2007**, *306*, 133–139. [CrossRef] [PubMed]
53. Guo, Q.; Mori, T.; Jiang, Y.; Hu, C.; Osaki, Y.; Yoneki, Y.; Sun, Y.; Hosoya, T.; Kawamata, A.; Ogawa, S.; et al. Methylglyoxal Contributes to the Development of Insulin Resistance and Salt Sensitivity in Sprague-Dawley Rats. *J. Hypertens.* **2009**, *27*, 1664–1671. [CrossRef] [PubMed]
54. Chen, J.; Jing, J.; Yu, S.; Song, M.; Tan, H.; Cui, B.; Huang, L. Advanced Glycation Endproducts Induce Apoptosis of Endothelial Progenitor Cells by Activating Receptor RAGE and NADPH Oxidase/JNK Signaling Axis. *Am. J. Transl. Res.* **2016**, *8*, 2169–2178.
55. Akhter, F.; Chen, D.; Akhter, A.; Sosunov, A.A.; Chen, A.; McKhann, G.M.; Yan, S.F.; Yan, S.S. High Dietary Advanced Glycation End Products Impair Mitochondrial and Cognitive Function. *J. Alzheimer's Dis.* **2020**, *76*, 165–178. [CrossRef]
56. Zhang, Y.; Huang, X.; Yuan, Y. Linagliptin Protects Human Chondrogenic ATDC5 Cells against Advanced Glycation End Products (AGEs)-Induced Apoptosis via a Mitochondria-Dependent Pathway. *Chem. Biol. Interact.* **2020**, *315*, 108901. [CrossRef]
57. Coughlan, M.T.; Yap, F.Y.T.; Tong, D.C.K.; Andrikopoulos, S.; Gasser, A.; Thallas-Bonke, V.; Webster, D.E.; Miyazaki, J.I.; Kay, T.W.; Slattery, R.M.; et al. Advanced Glycation End Products Are Direct Modulators of β-Cell Function. *Diabetes* **2011**, *60*, 2523–2532. [CrossRef]
58. Stephenson, J.; Heslehurst, N.; Hall, J.; Schoenaker, D.A.J.M.; Hutchinson, J.; Cade, J.E.; Poston, L.; Barrett, G.; Crozier, S.R.; Barker, M.; et al. Before the Beginning: Nutrition and Lifestyle in the Preconception Period and Its Importance for Future Health. *Lancet* **2018**, *391*, 1830–1841. [CrossRef]

59. Musial, B.; Vaughan, O.R.; Fernandez-Twinn, D.S.; Voshol, P.; Ozanne, S.E.; Fowden, A.L.; Sferruzzi-Perri, A.N. A Western-Style Obesogenic Diet Alters Maternal Metabolic Physiology with Consequences for Fetal Nutrient Acquisition in Mice. *J. Physiol.* **2017**, *595*, 4875–4892. [CrossRef]
60. Kereliuk, S.M.; Brawerman, G.M.; Dolinsky, V.W. Maternal Macronutrient Consumption and the Developmental Origins of Metabolic Disease in the Offspring. *Int. J. Mol. Sci.* **2017**, *18*, 1451. [CrossRef]
61. Grilo, L.F.; Diniz, M.S.; Tocantins, C.; Areia, A.L.; Pereira, S.P. The Endocrine–Metabolic Axis Regulation in Offspring Exposed to Maternal Obesity—Cause or Consequence in Metabolic Disease Programming? *Obesities* **2022**, *2*, 236–255. [CrossRef]
62. Cordero, P.; Vinciguerra, M.; Oben, J.A. *Maternal Perinatal Nutrition and Offspring Programming*; Elsevier Inc.: Amsterdam, The Netherlands, 2020; ISBN 9780128045725.
63. Barker, D.J.P. The Developmental Origins of Adult Disease. *J. Am. Coll. Nutr.* **2004**, *23*, 588S–595S. [CrossRef] [PubMed]
64. Lopes, G.A.D.; Ribeiro, V.L.B.; Barbisan, L.F.; Marchesan Rodrigues, M.A. Fetal Developmental Programing: Insights from Human Studies and Experimental Models. *J. Matern.-Fetal Neonatal Med.* **2017**, *30*, 722–728. [CrossRef] [PubMed]
65. Balakumar, M.; Raji, L.; Prabhu, D.; Sathishkumar, C.; Prabu, P.; Mohan, V.; Balasubramanyam, M. High-Fructose Diet Is as Detrimental as High-Fat Diet in the Induction of Insulin Resistance and Diabetes Mediated by Hepatic/Pancreatic Endoplasmic Reticulum (ER) Stress. *Mol. Cell. Biochem.* **2016**, *423*, 93–104. [CrossRef]
66. Saad, A.F.; Dickerson, J.; Kechichian, T.B.; Yin, H.; Gamble, P.; Salazar, A.; Patrikeev, I.; Motamedi, M.; Saade, G.R.; Costantine, M.M. High-Fructose Diet in Pregnancy Leads to Fetal Programming of Hypertension, Insulin Resistance, and Obesity in Adult Offspring. *Am. J. Obstet. Gynecol.* **2016**, *215*, 378.e1–378.e6. [CrossRef]
67. Toop, C.R.; Muhlhausler, B.S.; O'Dea, K.; Gentili, S. Impact of Perinatal Exposure to Sucrose or High Fructose Corn Syrup (HFCS-55) on Adiposity and Hepatic Lipid Composition in Rat Offspring. *J. Physiol.* **2017**, *595*, 4379–4398. [CrossRef]
68. Thompson, M.D.; Debosch, B.J. Maternal Fructose Diet-Induced Developmental Programming. *Nutrients* **2021**, *13*, 3278. [CrossRef]
69. Koo, S.; Kim, M.; Cho, H.M.; Kim, I. Maternal High-Fructose Intake during Pregnancy and Lactation Induces Metabolic Syndrome in Adult Offspring. *Nutr. Res. Pract.* **2021**, *15*, 160–172. [CrossRef]
70. Rodríguez, L.; Otero, P.; Panadero, M.I.; Rodrigo, S.; Álvarez-Millán, J.J.; Bocos, C. Maternal Fructose Intake Induces Insulin Resistance and Oxidative Stress in Male, but Not Female, Offspring. *J. Nutr. Metab.* **2015**, *2015*, 158091. [CrossRef]
71. Rodríguez, L.; Panadero, M.I.; Roglans, N.; Otero, P.; Rodrigo, S.; Álvarez-Millán, J.J.; Laguna, J.C.; Bocos, C. Fructose Only in Pregnancy Provokes Hyperinsulinemia, Hypoadiponectinemia, and Impaired Insulin Signaling in Adult Male, but Not Female, Progeny. *Eur. J. Nutr.* **2016**, *55*, 665–674. [CrossRef]
72. Clayton, Z.E.; Vickers, M.H.; Bernal, A.; Yap, C.; Sloboda, D.M. Early Life Exposure to Fructose Alters Maternal, Fetal and Neonatal Hepatic Gene Expression and Leads to Sex-Dependent Changes in Lipid Metabolism in Rat Offspring. *PLoS ONE* **2015**, *10*, e0141962. [CrossRef] [PubMed]
73. Mukai, Y.; Ozaki, H.; Serita, Y.; Sato, S. Maternal Fructose Intake during Pregnancy Modulates Hepatic and Hypothalamic AMP-Activated Protein Kinase Signalling in a Sex-Specific Manner in Offspring. *Clin. Exp. Pharmacol. Physiol.* **2014**, *41*, 331–337. [CrossRef] [PubMed]
74. Tain, Y.L.; Chan, J.Y.H.; Hsu, C.N. Maternal Fructose Intake Affects Transcriptome Changes and Programmed Hypertension in Offspring in Later Life. *Nutrients* **2016**, *8*, 757. [CrossRef] [PubMed]
75. Pascual, F.; Coleman, R.A. Fuel Availability and Fate in Cardiac Metabolism: A Tale of Two Substrates. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **2016**, *1861*, 1425–1433. [CrossRef]
76. Leu, S.; Wu, K.L.H.; Lee, W.C.; Tain, Y.L.; Chan, J.Y.H. Maternal Fructose Intake Exacerbates Cardiac Remodeling in Offspring with Ventricular Pressure Overload. *Nutrients* **2021**, *13*, 3267. [CrossRef]
77. Torrealba, N.; Aranguiz, P.; Alonso, C.; Rothermel, B.A.; Lavandero, S. Mitochondria in Structural and Functional Cardiac Remodeling. *Adv. Exp. Med. Biol.* **2017**, *982*, 277–306. [CrossRef]
78. Mericq, V.; Piccardo, C.; Cai, W.; Chen, X.; Zhu, L.; Striker, G.E.; Vlassara, H.; Uribarri, J. Maternally Transmitted and Food-Derived Glycotoxins: A Factor Preconditioning the Young to Diabetes? *Diabetes Care* **2010**, *33*, 2232–2237. [CrossRef] [PubMed]
79. Gupta, A.; Uribarri, J. Dietary Advanced Glycation End Products and Their Potential Role in Cardiometabolic Disease in Children. *Horm. Res. Paediatr.* **2016**, *85*, 291–300. [CrossRef] [PubMed]
80. Csongová, M.; Gurecká, R.; Koborová, I.; Celec, P.; Domonkos, E.; Uličná, O.; Somoza, V.; Šebeková, K. The Effects of a Maternal Advanced Glycation End Product-Rich Diet on Somatic Features, Reflex Ontogeny and Metabolic Parameters of Offspring Mice. *Food Funct.* **2018**, *9*, 3432–3446. [CrossRef]
81. Francisco, F.A.; Barella, L.F.; Silveira, S.D.S.; Saavedra, L.P.J.; Prates, K.V.; Alves, V.S.; Franco, C.C.D.S.; Miranda, R.A.; Ribeiro, T.A.; Tófolo, L.P.; et al. Methylglyoxal Treatment in Lactating Mothers Leads to Type 2 Diabetes Phenotype in Male Rat Offspring at Adulthood. *Eur. J. Nutr.* **2018**, *57*, 477–486. [CrossRef]
82. Mortensen, O.H.; Larsen, L.H.; Ørstrup, L.K.H.; Hansen, L.H.L.; Grunnet, N.; Quistorff, B. Developmental Programming by High Fructose Decreases Phosphorylation Efficiency in Aging Offspring Brain Mitochondria, Correlating with Enhanced UCP5 Expression. *J. Cereb. Blood Flow Metab.* **2014**, *34*, 1205–1211. [CrossRef] [PubMed]
83. Yamada, H.; Munetsuna, E.; Yamazaki, M.; Mizuno, G.; Sadamoto, N.; Ando, Y.; Fujii, R.; Shiogama, K.; Ishikawa, H.; Suzuki, K.; et al. Maternal Fructose–Induced Oxidative Stress Occurs via Tfam and Ucp5 Epigenetic Regulation in Offspring Hippocampi. *FASEB J.* **2019**, *33*, 11431–11442. [CrossRef] [PubMed]

84. Bridges, H.R.; Jones, A.J.Y.; Pollak, M.N.; Hirst, J. Effects of Metformin and Other Biguanides on Oxidative Phosphorylation in Mitochondria. *Biochem. J.* **2014**, *462*, 475–487. [CrossRef] [PubMed]
85. Meng, Q.; Qi, X.; Fu, Y.; Chen, Q.; Cheng, P.; Yu, X.; Sun, X.; Wu, J.; Li, W.; Zhang, Q.; et al. Flavonoids Extracted from Mulberry (*Morus alba* L.) Leaf Improve Skeletal Muscle Mitochondrial Function by Activating AMPK in Type 2 Diabetes. *J. Ethnopharmacol.* **2020**, *248*, 112326. [CrossRef]
86. Gutierrez, J.A.; Liu, W.; Perez, S.; Xing, G.; Sonnenberg, G.; Kou, K.; Blatnik, M.; Allen, R.; Weng, Y.; Vera, N.B.; et al. Pharmacologic Inhibition of Ketohexokinase Prevents Fructose-Induced Metabolic Dysfunction. *Mol. Metab.* **2021**, *48*, 101196. [CrossRef]
87. van Poelje, P.D.; Potter, S.C.; Erion, M.D. Fructose-1, 6-Bisphosphatase Inhibitors for Reducing Excessive Endogenous Glucose Production in Type 2 Diabetes. *Handb. Exp. Pharmacol.* **2011**, *203*, 279–301. [CrossRef]
88. Mazzoli, A.; Spagnuolo, M.S.; Nazzaro, M.; Gatto, C.; Iossa, S.; Cigliano, L. Fructose Removal from the Diet Reverses Inflammation, Mitochondrial Dysfunction, and Oxidative Stress in Hippocampus. *Antioxidants* **2021**, *10*, 487. [CrossRef]
89. Huang, H.M.; Wu, C.W.; Chen, I.C.; Lee, Y.C.; Huang, Y.S.; Hung, C.Y.; Wu, K.L.H. Maternal High-Fructose Diet Induced Early-Onset Retinopathy via the Suppression of Synaptic Plasticity Mediated by Mitochondrial Dysfunction. *Am. J. Physiol. Endocrinol. Metab.* **2021**, *320*, E1173–E1182. [CrossRef]