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Opinion

Dietary Sugars during Critical Phases of Development and Long-Term Risk of Non-Communicable Diseases

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Abstract: Obesity and the intake of high-sugar diets have dramatically increased in recent decades. However, it is still uncertain how sugar intake during the critical development phase affects the long-term health of children. In this context, the Developmental Origins of Health and Disease (DOHaD) concept established a correlation between early life environment and the development of cardiometabolic diseases in adulthood. This review summarizes the current knowledge about the consequences of sugar intake during the critical development phase for the onset of non-communicable diseases (NCDs). We found evidence that increased sugar intake during pregnancy contributes to maternal obesity and many cardiometabolic dysfunctions in the offspring. Furthermore, dietary sugar during the suckling period provokes the obese phenotype in adulthood. Finally, high-sugar diet intake during childhood induces metabolic syndrome and depressive-like behavior.

Keywords: DOHaD; pregnancy; lactation; childhood; obesity

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1. Introduction

It is evident that obesity is a public health concern around the world. According to the World Health Organization (WHO), worldwide obesity has nearly tripled since 1975, and there are around 2 billion adults who are overweight and 650 million who are obese. In 2016, it is estimated that more that 40 million children under the age of 5 years were overweight or obese. Moreover, between 1975 and 2016, the prevalence of obesity among children and adolescents increased from 4% to 18% [1].

Maternal and childhood obesity is linked to a range of adverse health outcomes later in life, as well as some negative societal outcomes. Recent studies have shown an association between nutritional insults during the initial phases of development and a long-term risk of non-communicable diseases (NCDs), including obesity, diabetes and cardiovascular diseases [2,3]. Thus, the developmental origins of the health and disease hypothesis (DOHaD) proposes a link between the fetal, early infant and puberty phases of life and the long-term development of cardiometabolic disorders [4]. This is why we consider the governmental and private strategies linked to the DOHaD concept one of our political priorities.

The main mechanisms, according to the DOHaD hypothesis, are epigenetic adaptations, such as DNA methylation, histone acetylation and differential small RNAs expression, that occur during critical phases of development in response to environmental factors like nutritional disorders [5].

In general, increased calorie intake and decreased physical activity play a key role in obesity onset and in the most common causes of NCDs [6]. It has been noted that the intake of dietary sugars, mainly sugar-sweetened beverages, increases overall energy intake, leading to a reduced intake of healthy foods containing adequate calories, contributing to body weight gain and increased risk of NCDs [7]. Recently, a study showed that male mice

fed a standard diet but drinking sweetened water (60 mg/mL sucrose solution) for sixteen weeks, presented a significant increase in fat mass, leading to increased plasma LDL and insulin, glucose intolerance and hepatic steatosis [8].

Sugar enriched diets contain high levels of monosaccharides (glucose, fructose and galactose) and disaccharides (sucrose, maltose and lactose), which are named as free sugars, and also contain polysaccharides such as starch. In this sense, there is a growing concern about the intake of foods whose caloric content is basically composed by added sugars, mainly sugar-sweetened beverages. The WHO recommends that the intake of free sugars be less than 5% of total energy intake [7]. However, this amount is often exceeded with sugar-sweetened beverages intake. The free sugars are quickly absorbed and contribute significantly to high blood glucose levels, leading to increased insulinemia. In the long term, this condition leads to the development of glucose intolerance and insulin resistance [9]. Furthermore, a high dietary sugar intake contributes to the formation of endogenous advanced glycation end products (AGEs). A high fructose intake is related to AGE accumulation in different tissues, which leads to insulin resistance and dyslipidemia [10]. Studies have reported that perinatal exposure to AGEs during pregnancy and lactation is one of the factors causing metabolic programming, increasing the risk of developing NCDs in adulthood [11].

Unfortunately, it has been reported that the intake of sugary foods is high among children and adolescents [7]. Glucose is the main source of energy to the central nervous system (CNS), and high-sugar diets can provoke an overdrive mode in the CNS. When the CNS is overstimulated by excess sugars, it leads to hyperactivity and mood swings. However, these behavioral changes are not the only short-term consequences. Some evidence suggests that this hyperactivity in the CNS in adolescents is linked to the anxiogenic state in adulthood. Sugar also causes an addictive effect, stimulating neurons of the limbic system, which reinforces further sugar consumption [12].

In this review, we provide updated knowledge about the intake of dietary sugars and their risk for NCDs onset in adults and children. As well as highlighting the importance of recognizing the rapidly growing epidemic of overweight and obesity during critical phases of development, we also explore the adaptive mechanisms of phenotypic changes early in life and the long-term effects supported by the DOHaD concept.

2. Materials and Methods

In this study the relationship between high-sugar diets and DOHaD were assessed by comprehensive literature review. Through advanced search on PubMed, Medline, Scopus and Google Scholar, manuscripts published between January 1990 and December 2022 were assessed and filtered by the following search strategy: "(sugar) AND ((pregnancy) OR (lactation) OR (childhood) OR (puberty) OR (DOHaD) OR (obesity) OR (diabetes) OR (non-communicable diseases))".

The inclusion criteria of the selected manuscripts were studies that showed some kind of relationship between the early intake of a sugary diet and non-communicable diseases in adult life.

3. Dietary Sugars and Pregnancy

Adequate maternal body weight gain during pregnancy is important for ensuring the healthy development of the fetus. Maternal nutrition is one of the main factors that impairs body weight gain of the mother during gestational period. Few studies have specifically evaluated the effects of high-sugar intake on gestational body weight gain. In a cohort study with Danish women, Maslova et al. found that sugar intake during pregnancy was correlated with excessive gestational weight gain (GWG). The authors evaluated the relation between protein/carbohydrate (P/C) ratio and added sugar intake during pregnancy and GWG. This study shows that a high P/C ratio is an important determinant of reduced GWG. On the other hand, high-sugar intake was related to increased GWG, as stated by the authors "added sugar consumption was strongly associated with GWG

(Q5 vs. Q1: 34, 95% CI 28 to 40 g/week)" [13]. In another study, authors have shown that intake of added sugars food, including sweets, snacks, cakes and soft drinks, were strongly associated with body weight gain in pregnant woman, in which women who consumed sweets ≥ 2/day gained an additional 5.4 kg (95% CI 2.1–8.7). The authors also note that reducing the added sugars intake is more important to prevent GWG than reducing the intake of other nutrients, such as protein or saturated fat [14].

Independent of maternal body weight gain or gestational obesity, excessive sugar intake during pregnancy is associated with pregnancy complications, such as gestational diabetes, preeclampsia and premature delivery. The main mechanisms involved in the effects of sugar intake on pregnancy complications are insulin sensitivity and inflammation. In this review, the focus is not exclusively on maternal harm due to greater weight gain during pregnancy, but rather on the consequences for the children of mothers who ingest high-sugar diets. In this sense, Catherine et al. showed that offspring born from mothers fed with 50% fructose were hyperglycemic at birth [15].

The ingestion of high-sugar diets during the gestational period is not only harmful to the pregnant person's or to the fetus' health during uterine life. According to the DOHaD concept, pregnancy is an important stage of ontogenetic plasticity. Arima and Fukuoka have shown that birth weight is inversely associated with the incidence of cardiovascular disease. The authors also presented some studies that point out that maternal malnutrition during pregnancy causes long-term consequences to the offspring, which includes several cardiometabolic dysfunctions [16].

During fetal development, intense neurogenesis occurs. In addition, environmental and nutritional disruptions can interfere with the CNS development, especially in the hypothalamus, which can compromise its function. The hypothalamic-pituitary-adrenal (HPA) axis is dramatically affected during fetal development. Changes in the HPA axis during pregnancy can result in dysfunctions in the release and action of glucocorticoids (corticosterone in rodents and cortisol in humans). It was observed that the offspring from rats fed a standard chow plus 20% (w/v) fructose in drinking water during gestation showed increased circulating corticosterone, and enhanced DNA methylation of 5α-reductase 1 promoter region in the adrenal of the offspring at postnatal day 160 [17]. Rodrigo et al. investigated whether maternal fructose intake (10% w/v in drinking water) by pregnant rats throughout gestation produces changes in the cholesterol metabolism of progeny. The authors observed different responses between the sexes, the male offspring from fructose-fed mothers had higher plasma HDL-cholesterol levels, whereas the female offspring from fructose-fed mothers had lower levels of non-HDL cholesterol. An important result of this study was the increase in the DNA methylation of Liver X-receptor (LXRα) in males from fructose-fed mothers, which decreased in the corresponding group of females. LXRα is an important regulator of cholesterol metabolism [18]. Rodriquez et al. also demonstrated that maternal fructose intake (10% w/v in drinking water) during pregnancy affects maternal and fetal leptin signaling [19]. Vickers et al. similarly demonstrated that offspring from fructose-fed mothers (20% of caloric intake from fructose) had impaired metabolic function, hyperglycemia and hyperleptinemia [20]. Together, these effects may predispose the offspring to obesity and metabolic syndrome later in life, with consequent development of cardiovascular diseases and diabetes.

4. Dietary Sugars and Lactation/Infancy

For rodents, it is perhaps possible that lactation is one of the most critical phases of development. This occurs because the neural differentiation of the circuitry responsible for appetite and energy expenditure begins in the last week of gestation and continues during lactation in rodents [21]. Around the first 14 days after birth, there is an increase in the leptin levels on the blood, which is called a postnatal leptin surge. Therefore, leptin levels during lactation are crucial for the offspring's CNS development [22].

The WHO recommends exclusive breastfeeding until 6 months of life and complementary breastfeeding until the age of 2 years [23]. It has been observed that breastfeeding

prevents several diseases such as diabetes, multiple sclerosis, cardiovascular and celiac diseases [24]. Breast milk composition depends on maternal nutrition and there is evidence that breast milk may also be a source of glycotoxins during lactation. Studies have shown that the neonatal intake of breast milk from diabetic mothers was related to overweight and glucose intolerance in the offspring [25].

Our group published a study where it was observed that the offspring of diet-induced obese mothers (DIO, containing sucrose and sweetened condensed milk) throughout the suckling period, presented in the obese phenotype in adulthood. Maternal DIO produces subsequent changes in breast milk composition, increasing carbohydrates and lipids content. Furthermore, DIO offspring developed leptin and insulin hypothalamic resistance and peripheral glucose dyshomeostasis, leading to changes in the morphology of the endocrine pancreas, with compensatory pancreatic β-cell hypertrophy [26].

During the first years of life, the central nervous system shows great plasticity and is subject to changes caused by maternal nutritional impairments that can affect the infant's learning. Berger et al. evaluated whether infant cognitive development can be negatively affected maternal fructose consumption. The authors showed that maternal fructose intake during the first postnatal month was negatively correlated with infant cognitive development at two postnatal years [27].

As an effect of the higher consumption of sugars or the formula-feeding of infants, increased levels of glycotoxins such as methylglyoxal (MG) are very harmful to health. Francisco et al. [28] evaluated whether maternal MG exposure during lactation programs the progeny to metabolic dysfunction later in life. MG mothers had elevated levels of glucose, triglycerides, cholesterol and fructosamine and low insulin in the breast milk. Furthermore, MG offspring had the obese phenotype in adulthood, as well as glucose intolerance and impaired β-cell function. They also showed increased risk of cardiovascular disease [28]. On the other hand, a sugar restricted diet during neonatal period prevented the development of type 1 diabetes in the offspring of non-obese diabetic mice [29]. In addition, infant formulas are rich in sugars and proteins, and their industrial production includes heat treatment, which can increase the amount of the AGEs, such as MG. In humans, Rose et al. [30] described that formula-fed children were more prone to choose unhealthy foods. Additionally, Weijs et al. [31] have shown that a high intake of sugar-containing beverages in the first year of life were correlated to a higher risk of developing obesity/overweight in 8-year-old children.

Due to the proximity of the puberty period to the lactation period in animal models, the keywords "infancy" or "childhood" rarely return results. In humans, due to the difficulty of obtaining results through questionnaires, there are few studies of cohorts that evaluate the long-term effects of high sugar intake during the childhood.

5. Dietary Sugars and Puberty

The increased obesity rates among children and adolescents are a great public health problem. In the United States, more than 40% of children and adolescents are overweight or obese. Puberty is an important ontogenetic window due to several morphophysiological changes that occur in this phase. This period is marked by increased of individual freedom, dietary and lifestyle choices, associated with risky behaviors such as smoking and alcohol consumption [32]. In response to concerns about adolescent food choices, the WHO [7] has reduced the recommended intake of free sugars to less than 5% of total energy intake.

According to the Dietary Guidelines for Americans (DGA), adolescent (14 to 18 years old) girls require about 1800 to 2400 calories per day and boys need about 2000 to 3200 calories per day. The foods that make up a healthy dietary pattern include: vegetables, beans, peas, lentils and starchy foods; fruits, especially whole fruit; grains; dairy, including fat-free or low-fat milk, yogurt and cheese, and/or lactose-free versions and fortified soy beverages; protein foods, including lean meats, poultry and eggs; seafood; nuts, seeds and soy products; and oils, including vegetable oils and oils in food, such as seafood and nuts [33]. In addition to physical inactivity, malnutrition among adolescents is

the main cause of the increase in the number of obese young people. In this sense, the high intake of free sugars contributes to the increase in NCDs.

Harrell et al. showed that a high-fructose diet intake during adolescence increases neuroinflammation and depressive-like behaviors. Furthermore, the authors also showed that feeding male rats a sugar-rich diet (55% *w*/*w* energy from fructose), provoked elevated TNFα and corticosterone levels [34].

In a recent study, the authors presented the fact that non-natural food intake, of foods containing high fructose levels, was associated with elevated diastolic blood pressure (DBP) in adolescent girls. The authors emphasize that the consumption of natural foods containing fructose, (e.g., fruits) does not impact blood pressure and should continue as part of a healthy diet [35]. On the other hand, Schwimmer et al. observed that adolescent boys with NAFLD had a significant improvement in hepatic steatosis after 8 weeks of eating a diet composed of less than 3% daily calories from free sugar [36]. In the same sense, in another study, the authors showed that the intake of sugars by adolescents in the US is associated with low HDL cholesterol levels, high LDL cholesterol and triglycerides and overweight/obese, known to increase metabolic syndrome risk [37]. In a study that examined the association between added sugar intake and metabolic syndrome, US adolescents (1623), aged 12–19 years, were evaluated. Rodríguez et al. showed that added sugar intake is directly associated with metabolic syndrome among non-Hispanic white, non-Hispanic black and Mexican-American US adolescents, independent of total energy intake, physical activity or body mass index (BMI) score [38].

6. Conclusions, Future Perspectives and Limitations

Here, in this review, we explored evidence of how exposure to high-sugar diets can contribute to the obese phenotype and lead to the development of NCDs later in life. In fact, it could be observed that an increased intake of dietary sugars during pregnancy, lactation, childhood and puberty are all risk factors for the development of cardiometabolic dysfunctions, with serious implications for aging, as shown in Figure 1.

It is evident that the DOHaD concept is gaining great notoriety around the world. Scientific societies and events have been organized with the aim of bringing together researchers and knowledge about how the first 1000 days after birth can be decisive throughout life, especially during aging. It has also been well known that sexual dimorphism is a factor that differentiates phenotypic responses throughout the critical phases of development. However, many gaps still need to be filled in order to better understand how perinatal life and puberty can be decisive for programming a healthy phenotype throughout life. It remains unknown how increased sugar intake during critical phases of development affects: (1) release of GnRH, which is mainly stimulated by kisspeptin; (2) the release of FSH and LH and their trophic effects on the gonads, and whether this differential release interferes with puberty onset; and (3) the ghrelin release and its actions on the CNS, as well as the release of GH, since blood glucose or dietary sugars interfere with the release of these two hormones. Finally, we hope that more experimental and cohort studies under the DOHaD concept can contribute to improving public policies and updating guidelines to provide recommendations about the risks of the intake of sugars, and can also contribute to elaborating interventions for improving healthy development.

The main limitation of this study is that, compared to other risk factors such as high-fat diet, relatively few studies have been dedicated to investigating the effects of dietary sugars during critical phases of development. Studies using animal models have demonstrated interesting results; however, the direct applicability of these protocols to humans is almost impossible. In this sense, more experimental studies are necessary to unravel late clinical interventions for mitigating the effects of early-life high sugar consumption or high glucose environment exposure.

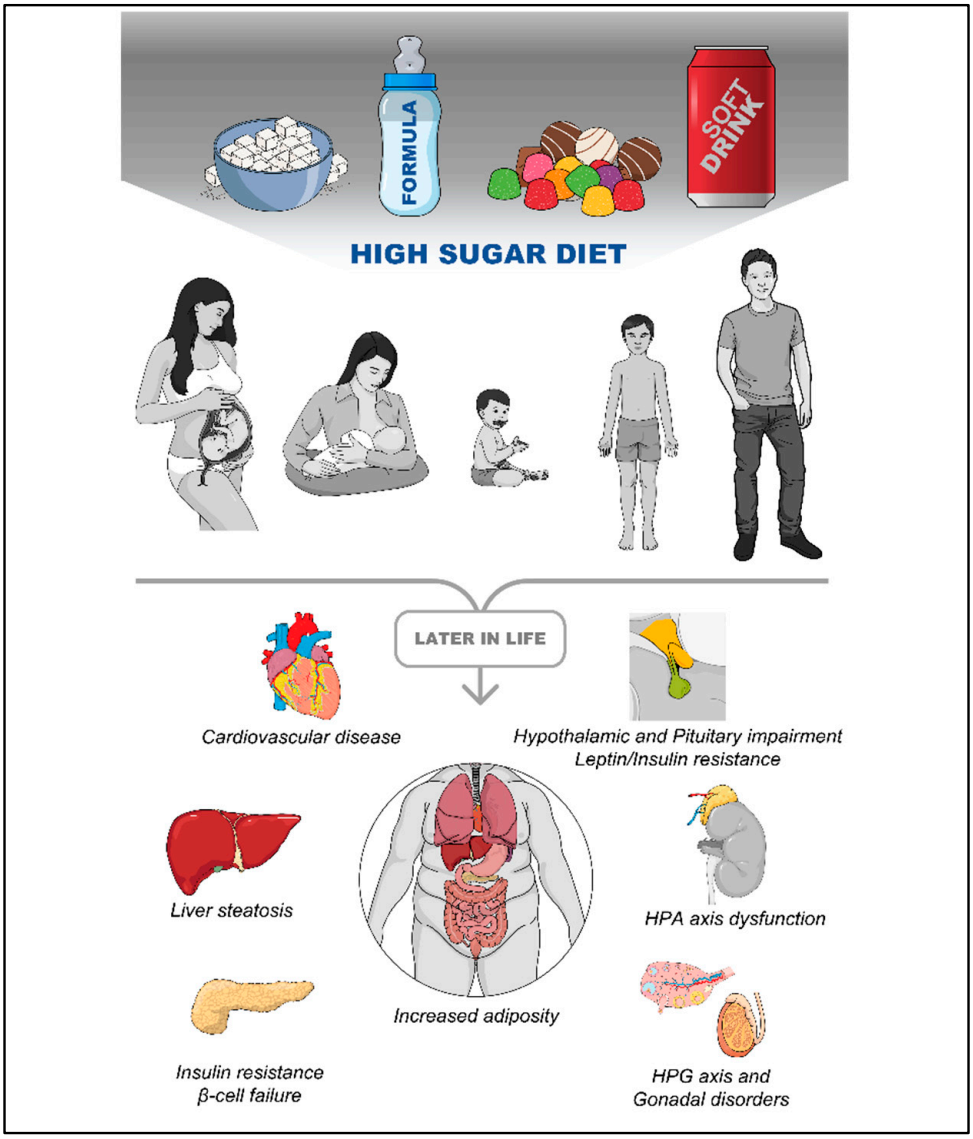

Figure 1. Schematic representation of how dietary sugars during critical phases of development affect healthy development, leading to an obese phenotype in adulthood, with many dysfunctions of homeostasis.

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