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Review

Effect of polyphenols intake on obesity-induced maternal programming.

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Abstract: Obesity is a complex chronic disease characterized by excess of body fat. It represents a significant public health problem due to the health-related risk factors. There are growing evidences showing that maternal obesity can program the offspring, which influence neonatal phenotype and predispose offspring to a higher prevalence of metabolic disorders such as obesity. This increased risk may also be epigenetically transmitted across generations. Thus, there is an urgent need to find effective reprogramming approaches in order to resume normal fetal development. Polyphenols are bioactive compounds found in fruits and vegetables that exert their anti-obesity effect through its powerful anti-oxidant and anti-inflammatory activities. Polyphenols supplementation has been proven to counteract the deleterious effects of maternal obesity programming on offspring. Indeed, some polyphenols can cross the placenta and protect the fetal predisposition against obesity. The present review summarizes the effects of dietary polyphenols on obesity-induced maternal reprogramming as an offspring anti-obesity approach.

Keywords: Polyphenol, obesity, maternal programming.

1. Introduction

Obesity is a complex chronic disease, characterized by excess body fat. It is considered as one of the main public health problems in the world, and affects not only industrialized nations, but also developing countries. Epidemiological data presented by the World Health Organization (WHO) found that since 1975, obesity has almost tripled and at least 2.8 million people die annually as a result of complications from obesity or overweight. Despite the current public awareness of the consequences of obesity, its incidence continues to rise, and is distributed in almost all ethnicities and in both sexes, mainly affecting the population aged 25 to 44 years [1].

Etiology of obesity is multifactorial and involves an interaction between genetic and environmental factors [2]. It is characterized as white adipose tissue (WAT) expansion, and in general results from an energy imbalance caused by an increase in caloric intake coupled with a decrease in daily energy expenditure [3,4]. The excess of energy is stored as triacylglycerols in adipocytes and, through the processes of hyperplasia or hypertrophy of these cells, there is an expansion of body fat deposits, an increase in the concentrations of free circulating fatty acids, peptides, inflammatory cytokines and adipokines, resulting in metabolic disorders such as diabetes, metabolic syndrome, hepatic steatosis, atherosclerosis and dyslipidemia, conditions that also contribute to the cardiometabolic risk [5,6].

Maternal obesity also has different clinical implications, and is associated with significant health risks to both the mother and the newborn. Of note, in animal models, high fat diet (HFD) intake during the pregnancy may predispose offspring to a higher

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prevalence of postnatal metabolic inflammatory disorders such as obesity. In this sense, the well-known anti-inflammatory activity of polyphenols could be considered as a reprogramming strategy against maternal obesity-induced adversities. Thus, the present review summarizes the effects of dietary polyphenols on obesity-induced maternal reprogramming as an offspring anti-obesity approach.

2. Obesity and maternal programming

It has been described that nutritional, hormonal, and environmental changes in critical periods of life (such as pregnancy and lactation) are strongly associated with the appearance of diseases in adulthood. The physiological adaptations developed by the organism, as a survival strategy, could potentially become detrimental to the individual's health from the moment when adverse conditions are restored to normal levels. Although several studies have shown that these disorders can have origins even before birth, the mechanisms by which these changes occur are still not fully understood. This biological phenomenon was initially called as “metabolic programming” [7–9] and later as “ontogenetic plasticity”, as it is a more probabilistic than deterministic event [10].

Indeed, the phenomenon of programming or ontogenetic plasticity has been extensively studied for decades by several research groups around the world. Adequate nutrition is known to be essential during crucial periods of development, as it can act as an imprinting or priming factor, leading to physiological changes programming future diseases. The association between the observed changes in critical periods and disorders in adulthood gave rise to the “Barker hypothesis” then the Fetal Origin of Adult Disease, and now the Developmental Origins of Health and Disease (DOHaD) [11].

Several factors involved in disease-programming have already been described [12–15]. Among them, we highlight the maternal obesity, which has been widely associated with the birth of newborns who are more susceptible to the development of overweight and obesity [16,17]. Although the prevalence of obesity grows alarmingly and affects all age groups, it should be noted that approximately 39.7% of women between 20 and 39 years of age are obese in US (NCHS Data Brief No. 360, February 2020). This set of data shows that obesity is a serious concern vicious cycle that requires intensive research.

The maternal obesity has been linked to an increased abdominal fat and higher cardiometabolic risk (increased blood pressure, increased serum concentrations of triglycerides, LDL-C and C-reactive protein and low concentrations of HDL-C) [18]. In animal studies, maternal obesity is associated with increased adiposity, hyperphagia, increased cholesterol and triglyceride concentrations and increased lipogenesis and a decrease in beta oxidation, leading to the development of hepatic steatosis on offspring [15,19]. Furthermore, it was already demonstrated that progeny of rats HFD-fed show changes such as weight gain, increased adiposity, hyperleptinemia, leptin resistance and hyperglycemia even immediately after weaning (21 days) [20].

The deleterious effects of maternal obesity occur during specific periods of fetal and postnatal development, where epigenetic memory can be modulated [21]. In murine models, adipogenesis is particularly active during the perinatal period, especially during the last week of gestation, and accelerates during the early postnatal life until the puppies are weaned. Thus, adipocyte stem cells are sensitive to maternal factors during lactation. In humans, adipose tissue growth and adipogenesis occur mainly before birth [9]. In both, the expansion of adipose tissue involves hyperplasia and hypertrophy. In adult mice, the adipocyte reservoir remains quite stable with 10 to 20% adipocyte renewal per month [22]. In humans, when the number of fat cells is established in adulthood (twice in obese individuals), they are renewed at an annual rate of 10%, regardless of body weight, which means that, in absolute numbers, the obese individuals renew twice as many fat cells per year. Furthermore, when obese individuals lose a considerable amount of weight, they maintain their high number of adipocytes, indicating that the adipose tissue has a numerical adipocyte memory, which are defined at the beginning of development [9].

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Thus, it is suggested that multiple epigenetic mechanisms are involved in "memorizing" the number of adipocytes.

3. Adipose tissue programming

Human adipose tissue development is an uninterrupted process that start early during embryogenesis [23]. The transcriptional cascade promoting adipogenesis is very complex and has been well-studied. Mechanically, during the development of adipose tissue, stem cells are sensitive to pro-adipogenic signals (hormones and metabolites). These signals induce a series of epigenomic changes in transcriptionally accessible regions of the genome, especially in adipogenic genes. The epigenomic profiles that are established during adipogenesis occur in two steps: (1) commitment of multipotent mesenchymal stem cells (MSCs) to differentiate into preadipocytes and (2) terminal differentiation [24].

In stem cells, transcription of pluripotency genes are active and adipogenic genes are repressed by the presence of repressive epigenetic marks (such as DNA methylation, H3K27me3 and H3K9me3) [9,24]. During the pre-adipogenic commitment, the pro-adipogenic genes are paused by the presence of bivalent histones H3K4me3 and H3K27me3 [25]. In the terminal differentiation, the bivalent state is converted to an active state associated with the recruitment of the first wave of transcription factors (such as, CCAAT Enhancer Binding Protein (C/EBP)β, glucocorticoid receptor, Sterol Regulatory Element Binding Transcription Factor 1 (SREBP-1C) and Zinc Finger Protein 423 (ZFP423)) [25–28]. These transcription factors, in turn, induce the reorganization of chromatin in open regions of the genome containing genes involved in the second wave of transcription factors, among which Peroxisome Proliferator Activated Receptor (PPAR)γ and CEBPα stand out. The second wave of transcription factors binds to chromatin and transcribes pro-adipogenic genes (such as Solute Carrier Family 2 Member 4 (SLC2A4), Adiponectin (ADIPOQ) and Leptin (LEP)) [25]. Adipogenesis occurs mainly during the development of adipose tissue (such as pregnancy and lactation). The adipose tissue, in turn, originates not only embryonic, but also postnatally until puberty. Early childhood and puberty are important periods for the development of a normal mass of adipose tissue. In fact, in humans and rodents, the number and size of adipocytes gradually increase until puberty under physiological conditions [29,30]. After puberty, the number and size of adipocytes remain stable [29,31].

Molecular evidence suggests that transmission of epigenetic marks (such as DNA methylation and changes in histones code) may be important in the children phenotypes. Recent studies suggest that the prevalence of obesity, diabetes and other chronic diseases may have an epigenetic inheritance [32–34]. Accordingly, it has been shown in rodents that maternal obesity modulates the expression of pro-adipogenic transcription factors, such as ZFP423, C/EBPβ and PPARγ, in the offspring, thus reprogramming adipogenesis. In a maternal obesity-programming model, it was observed that the offspring exhibited an increase in the levels of ZFP423 expression, which was associated with a reduced methylation in its promoter. At the weaning, it was observed that the high activity ZFP423 results in increased adipocyte differentiation, accelerated adipogenesis, and higher adiposity [35–37]. In addition, it is known that both DNA methylation and histone modifications can regulate PPARγ expression in adipose tissue. Thus, maternal obesity represses the expression of PPARγ2 through epigenetic mechanisms in the white adipose tissue of the offspring (Figure 1). Although it seems paradoxical, it is believed that the decline in the expression of this gene in adipose tissue may be an adaptive mechanism to prevent further accumulation of fat [38,39]. However, the persistently reduced expression of PPARγ2 is correlated with an increase in the expression of genes associated with fat accumulation (TNF receptor superfamily member 6 (Fas), diacylglycerol O-acyltransferase 2 (Dgat2), lipoprotein lipase (Lpl)), suggesting that, at least in part, such regulation should occur by additional signaling pathways independent of PPARγ [15]. In

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summary, maternal obesity may be associated with important epigenetic changes that explain the origin of obesity and other morbidities presented by the offspring.

4. Polyphenols effect on obesity and maternal programming

Beneficial effects of some diet natural components are attributed for their anti-inflammatory and anti-oxidant properties, and have been commonly used to treat and/or prevent diseases. In this sense, several studies highlight a broad range of biological activities to polyphenols [40,41].

Polyphenols are bioactive compounds found in fruits and vegetables naturally synthesized involved in plant defense as signaling molecules to protect plants against oxidative stress and ultraviolet radiation, or attracting pollinators [42]. Since chronic inflammation is known to be a major cause of different disorders such as obesity, cancer, diabetes type II, arthritis, neurodegenerative and cardiovascular diseases, many researches have been studying the beneficial role of polyphenols in reducing inflammation to treat chronic disorders [43]. These natural compounds are able to modulate the expression of several pro-inflammatory genes such as cytokines, nitric oxide synthases cyclooxygenase, lipoxygenase and, in addition to their anti-oxidant effect, contributes to the regulation of inflammatory signaling and support progress towards decreased metabolic disorders [44,45].

Polyphenols belong to a broad group of chemical substances, and can be divided into flavonoids, allied phenolic and polyphenolic compounds [46]. Some polyphenols such as anthocyanins are absorbed in the small intestine, while the unabsorbed polyphenols must be enzymatically hydrolyzed to be absorbed by epithelial cells [47]. Polyphenols exert their anti-obesity effect by their ability to interact, directly or indirectly, with adipose tissues and activate 5' adenosine monophosphate-activated protein kinase (AMPK) which results in the reduction of cholesterol, fatty acid synthesis, and triglyceride formation. Moreover, polyphenols can repress genes involved in adipocyte differentiation and triglyceride accumulation [48].

Epigallocatechin gallate (EGCG) is the most active and the main flavonoid compound in green tea. Strong emerging evidences have been shown the anti-obesity potential of EGCG. For instance, *in vitro* studies demonstrated that EGCG inhibits preadipocyte differentiation, decreases adipocyte proliferation, suppress lipogenesis, induces adipocyte apoptosis, and promotes lipolysis and fatty acid β-oxidation [49–51]. Additionally, EGCG decreased obesity and epididymal WAT weight in mice partially via activating AMPK pathway [52]. EGCG-mediated suppression of adipocyte differentiation may be attributed to MEK/ERK and PI3K/AKT pathways inhibition, which may lead to downregulation of PPARγ and C/EBPα which are known to be the mains regulators of adipogenesis [48].

Quercetin is one of the primary flavonoid compounds and widely exists in vegetables, tea, and fruits. It has been reported that quercetin suppressed lipid accumulation and nitric oxide production in zebrafish, and inhibited body weight, lipid accumulation and insulin resistance in mice [53]. In HFD-induced rodents, treatment with quercetin attenuated both obesity and insulin resistance, decreased the hepatic lipid accumulation by activating the expression of beta-oxidation related genes and decreased inflammation [54,55]. In human adipocyte models, quercetin significantly downregulated adipokines (i.e. Angiopoietin Like 4 (ANGPTL4) and Serpin Family E Member 1(SERPINE1, previously known as PAI-1)) and glycolysis-associated enzymes (i.e. Enolase 2, gamma neuronal (ENO2) and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 (PFKFB4)), which are closely related to obesity [56]. Mechanistically, *in vitro* and *in vivo* studies has demonstrated that quercetin is able to revert unfavorable epigenomic profiles associated with adipogenesis through the induction of chromatin remodeling and histone modifications, which leads to a decrease on C/EBPα and PPARγ gene expression [55].

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In HFD-fed rats, kaempferol decreased the accumulation of visceral fat and improved hyperlipidemia through the downregulation of SREBPs and upregulation of hepatic PPARα expression [57]. In obese HFD-induced mice, kaempferol protected against obesity and ameliorated hyperlipidemia partly through maintaining microbial diversity and modulating microbial communities, as well as downregulating PPARγ and SREBP-1C [58,59]. In another study, kaempferol modulated 3T3-L1 adipogenic differentiation through regulation of PPARα and C/EBPα [60,61].

Curcumin is a polyphenolic compound derived from the spice turmeric, which also showed the anti-obesity and anti-insulin sensitivity effects. Curcumin has been shown to suppress weight gain, improve insulin sensitivity, and prevent the development of diabetes in rodent models and prediabetic subjects [62]. Curcumin promoted beige adipogenesis and induced preadipocyte apoptosis in white adipocytes possibly mediated by AMPK, PPARγ, and C/EBPα [63,64]. In the differentiation process of rat MSCs, curcumin inhibited adipocyte differentiation and decreased expression of PPARγ and C/EBPα when cultured in the pro-adipogenic conditions [65].

Resveratrol, one of most studied polyphenolic compounds, is found in grapes, red wine and some berries. Due its powerful antioxidant and anti-inflammatory activity, resveratrol has been used in medicines, dietary supplements and as a functional food ingredient to achieve different health benefits. Several studies using adipocytes have demonstrated that resveratrol has an anti-obesity potential by negatively regulating white adipogenesis via inhibiting PPARγ, and C/EBPα [66], activating Sirtuin 1 (SIRT1) and (PPARγ Coactivator 1) PGC1α [67], attenuating white adipogenesis and lipid accumulation. Furthermore, their anti-obesity effect is achieved by inhibiting the transcriptional activities of PPARγ, inhibiting adipocyte differentiation and proliferation, inducing adipocyte apoptosis, decreasing lipogenesis, and promoting lipolysis and fatty acid oxidation [68–70].

It has been shown that maternal obesity alters functional properties of adipocytes from the fetal development [71] to adulthood [72], resulting in larger adipocytes and higher WAT mass [73]. Moreover, maternal obesity leads to increased cytokine production and placental-mediated inflammation, which could affect fetal development and may predispose progeny to subsequent obesity [74,75]. Since maternal obesity-induced metabolic programming has a profound impact on offspring, there is an urgent need to find effective reprogramming approaches in order to resume normal development. In this sense, supplementing with natural compounds such as polyphenols could be helpful in reprogramming of maternal adversities associated with obesity.

A study conducted by Kataoka, Norikura, & Sato, 2018 [76] showed that EGCG–rich green tea extract intake during lactation had a protective effects on kidney of HFD-feed adult offspring through the down-regulation of the epigenetic modulators, such as DNA methyltransferase 1 (DNMT1), ubiquitin like with PHD and ring finger domains 1 (UHRF1) and euchromatic histone lysine methyltransferase 2 (EHMT2), highlighting that offspring phenotype can be programmed by maternal polyphenols intake. In addition, EGCG treatment of rat embryos blocks Forkhead Box O3 (FOXO3A) activation and reverses AKT inhibition preventing hyperglycemia-induced embryopathy [77]. Similarly, soy isoflavone-rich diet during pregnancy may protect against cardiovascular diseases in the offspring through the stimulation of antioxidant enzymes and redox-sensitive gene expression [78].

Interestingly, Tain Y et al. [79] highlights the beneficial effects of resveratrol supplementation as an important reprogramming strategy against the development of metabolic syndrome-related disorders. The long-term effects of a combined maternal and postnatal HFD lead to metabolic disruption characterized by increased body weight, high levels of serum ALT, HDL, triglycerides, leptin, cholesterol, and angiotensin I and II, which could be ameliorated by resveratrol therapy [80]. It has been suggested that resveratrol could cross the placenta and affect its function through its anti-inflammatory [81] and anti-oxidant activities [82]. Animal studies showed that resveratrol may act as fat browning activator involving the secretion of many myokines and adipokines and suggest that maternal

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resveratrol supplementation may has a protective role against HFD-induced obesity [83,84]. Similarly, Zou et al. found that the resveratrol supplementation during pregnancy promotes a thermogenic program in BAT and WAT, and induces beige adipocyte development of WAT in male offspring [85]. Hsu et. al. [86] assessed the effect of maternal resveratrol intake of obese rats and found that resveratrol treatment restored adiponectin, AKT phosphorylation, brain-derived neurotrophic factor (BDNF) in male fetal brain; increased blood pressure, reduced increased body weight, peripheral insulin resistance in adult male offspring, further demonstrating that the intervention with this polyphenol may protects offspring against HFD-induced obesity. Another study using HFD-obese rats model [87] highlighted that the maternal resveratrol supplementation has a reprogramming role for progeny through lipid metabolic modulation. The authors showed that resveratrol treatment decreased lipogenesis and SIRT1 protein expression, attenuated leptin resistance, and increased lipolysis for progeny, resulting in an anti-obesity effect. Additionally, it has been shown that resveratrol supplementation prevents maternal glucose intolerance and lower blood glucose levels by increasing insulin secretion [88]. Figure 1 summarizes the obesity-induced maternal programming and how polyphenols intake could reprogram the epigenetic memory of adult offspring.

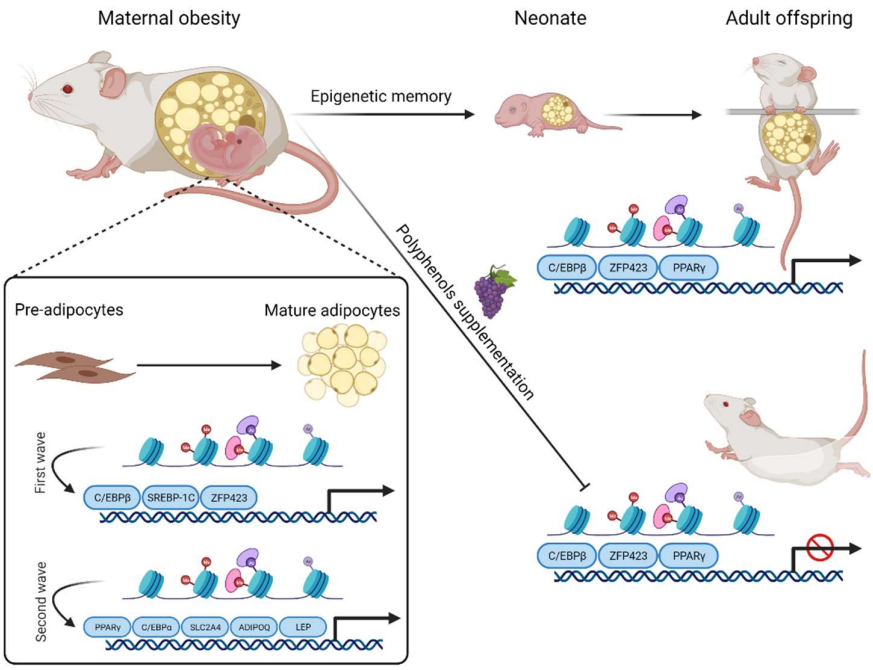

Figure 1. Schematic representation of polyphenols effect on obesity-induced maternal programming. In the adipocyte differentiation, the histone bivalent state is converted to an active state associated with the recruitment of the first wave of transcription factors (C/EBPβ, SREBP-1C and ZFP423). These transcription factors, in turn, induce the reorganization of chromatin in open regions of the genome containing genes involved in the second wave of transcription factors, among which PPARγ, CEBPα stand out. The second wave of transcription factors binds to chromatin and transcribes pro-adipogenic genes (SLC2A4, ADIPOQ and LEP). Maternal obesity modulates the expression of pro-adipogenic transcription factors, such as ZFP423, C/EBPβ and PPARγ during adipogenesis in the perinatal period and affects the offspring. Polyphenols supplementation could counteract the deleterious effects of maternal obesity programming on offspring by negatively regulating adipogenesis via inhibiting PPARγ, ZFP423 and C/EBPα.

5. Conclusions

The current evidences highlight the relevance of maternal obesity for the long-term metabolic health of the offspring. This review shows that there is increasing amount of experimental data pointing to the potential effects of polyphenols as a strategy to counteract the deleterious effects induced by maternal obesity. In general, the data reviewed here demonstrated that by supplementing pregnant and lactating obese animals with polyphenols including resveratrol, genistein, EGCG and anthocyanins lead to metabolic health reprogramming that ultimately decrease adiposity in of the offspring. Whether these observations translate to the human condition, remains to be determined. Further examination of obesity-induced maternal programming, especially in humans, is urgently needed and may help to develop polyphenol-based strategies to decrease the propagation of obesity across generations.

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