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Changes in Plasma's Oxidative Stress and Antioxidant Activity, Measured with Melatonin Levels, and its Relationship to Newborns from Obese and Diabetic Pregnancies

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Abstract

Researchers have reported that an overproduction of reactive oxygen species, together with lacking of antioxidant defense, promote oxidative damage involved in the etiology of various degenerative diseases. Women with normal pregnancies experience a physiological increase of oxidative stress without major cytotoxicity due to an effective antioxidant response. This delicate balance maybe disturbed with the presence of pro inflammatory diseases together with unhealthy lifestyles; such as excessive pregestational weight and high fatty and sugar diets (gluco- and lipotoxicity). We believe that disruption of prooxidant-antioxidant homeostasis may have a role on pregnancy adverse outcomes and unfavorable consequences for offspring in the short and long term. Especially for newborns from diabetic and obese mothers who may be exposed to metabolic programming changes with higher risk of developing degenerative diseases in their adult life. This minireview focuses on investigations that have found a relationship between increased oxidative damage during pregnancy and adverse fetal outcomes classified in normal, presence of hyperglycemia, and obese pregnancies; as well as recommendations for approaching these conditions including the novel potential findings of melatonin.

Keywords: Oxidative stress; Lipid peroxidation; Pregnancy; Antioxidants; Melatonin; Metabolic programming

Introduction

The increased incidence of obesity around the world is one of the most concerning problems in public health; especially during critical stages of growth and development, as it is in pregnancy and childhood. Only in the United States, 50% of women at a childbearing age (aged 20-30 years) are overweight or obese [1,2]. Consequently, the incidence of obesity and metabolic syndrome in childhood is also rising at an alarming rate [3-7], and therefore many researchers are focusing on investigations to determine its etiology and treatment for both mother and child.

The metabolic syndrome in adults has been defined as a group of risk factors for cardiovascular disease, including abdominal obesity, dyslipidemia, chronic hyperglycemia and hypertension [7]; whereas during childhood, obesity is a risk factor for metabolic syndrome in adulthood [8]. Therefore, prevention strategies are being studied from different perspectives so to improve quality of life and decrease the social and economic burden of degenerative diseases [9].

Recently, it has been proposed that during early stages of life, the fetus undergoes through various early metabolic programming processes, which can be changed permanently if an environmental event is present, like maternal malnutrition or excess pregestational weight, predisposing both mother and fetus to an increased risk of developing degenerative diseases, such as type 2 diabetes mellitus (T2DM) [10-12]. Since reactive oxygen and nitrogen species have been linked to different degenerative diseases associated to obesity, and that maternal obesity may affect the child's long term metabolic programming, the aim of this minireview is to present evidence on how overproduction of free radicals and a deficit of antioxidant defense during obese or diabetic pregnancies have impact on offspring's metabolic programming; and the use of melatonin as a targeted antioxidant to prevent such adverse outcomes.

Oxidative Stress

Definition

In healthy individuals, reactive oxygen species (ROS), reactive nitrogen species (RNS), and antioxidants coexist in a prooxidant-antioxidant delicate balance that leads to redox homeostasis [13-16]. This equilibrium is crucial for the maintenance of physiological functions of the organism and protection of cellular damage.

Nevertheless, the influence of exogenous insults such as unhealthy dietary habits, sedentarism and an excess body weight can alter such balance, inducing to oxidative stress and leading to a pro inflammatory state that has been linked to the etiology various degenerative diseases and aging [16-20]. During redox homeostasis, ROS play a physiological role as second messengers in intracellular signaling involved tissue repairment [16]; defense against infection, and are also important coordinators of the inflammatory response [21]. Oxidative and nitrosative stress occur when an overproduction of free radical species (FRs) and a deficit of non enzymatic and enzymatic antioxidant response disturb the cell's natural redox balance; one that is altered favoring the prooxidant side [16,19,22].

Free radicals can be defined as highly reactive and unstable molecules containing one or more unpaired electrons in atomic or

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molecular orbitals. They become stable by obtaining electrons from biological nearby non radical macromolecules, mainly nucleic acids, proteins, carbohydrates and lipids. This electron stealing causes a cascade of chain reactions resulting in cell injury, inhibiting their normal function, triggering apoptosis and necrosis. Thus, they have been linked with diabetes and cardiovascular diseases, as well as the ageing process [13,14,16,18]. Valko et al (2007) present a well extended review regarding ROS and human disease.

Reactive oxygen and nitrogen species

Reactive oxygen species are one of the major types of FRs; biologically, the most common are the superoxide anion radicals (where an addition of one electron to the dioxide molecule has taken place), followed by the hydroxyl and nitrogen anion radicals.

The first one is an oxygen molecule with an unpaired electron ($O_2^{\cdot-}$) that is generated by many different biological pathways and has a short half-life. The superoxide production occurs mainly within the mitochondria during the electron transport chain. Its toxicity comes when it's dismutaded by the superoxide dismutase (SOD) and forms hydrogen peroxide, that in the presence of free transition metals (Fe^{2+}, Cu^{+}) can generate a hydroxyl radical ($OH^{\cdot-}$) due to the Fenton reaction. Also, the $OH^{\cdot-}$ has a very short half-life (less than one nanosecond) [16,23]. The highly reactive hydroxyl probably accounts for most of the oxidative damage attributed to ROS, which plays a very important role in membrane polyunsaturated fatty acid (PUFA) lipid peroxidation [18].

The overproduction of RNS is called nitrosative stress. A pro oxidative reaction comes when nitric oxide free radical ($NO\cdot$) reacts with superoxide molecules forming a very strong pro oxidant (peroxynitrite) that can cause DNA fragmentation and lipid oxidation [16] leading to tissue damage by nitration of tyrosine bases in proteins [14,15].

Lipid peroxidation (LPO)

When stealing electrons from non radical molecules, the lipid peroxidation (LPO) chain reaction occurs, a typical example. This reaction occurs when the hydroxyl radical subtracts an electron from a nearby polyunsaturated fatty acid (LH) and at the end produces a carbon-centered lipid radical ($L^{\cdot}$) [16]. This last product can interact with molecular oxygen generating a lipid peroxyl radical ($LOO^{\cdot}$), that in the presence of antioxidants is reduced and therefore the redox homeostasis persists. If the antioxidant response is incapable of maintaining this balance, the process of lipid peroxidation occurs, increasing oxidative stress and thus cell and mitochondrial membrane damage [16,24].

Cellular injury and oxidative damage

Cells show a wide range of responses upon exposure to FRs, ranging from increased proliferation, prevention of cell division, senescence, necrosis, apoptosis, or cell death mechanisms with features of both [22]. During the cell's normal life, ROS are constantly generated under aerobic conditions. When inflammation happens, this process does not always imply a negative effect; here they can destroy invading pathogens and help modulating a superabundant inflammatory response under certain circumstances [22]. Importantly, oxidative stress (OS) is not equal to oxidative damage (OD); the first one represents an imbalance of the redox homeostasis, but the second one is the result not only from oxidative stress but also when the repair mechanisms tend to fail [21,22]. Oxidative damage can be defined as the biomolecular damage caused by an attack of reactive species upon the constituents of living organisms [22]. Amongst cellular organelles, mitochondria comes to high relevance due to its role in energy production by being involved in oxidative phosphorylation that drives ATP synthesis through cellular respiration; as well as gluconeogeneis, protein and urea synthesis, production of free radicals and apoptosis [25,26]. Its dysfunction has been associated to insulin resistance and β-cell dysfunction [27], thus to the development of T2DM.

Mitochondria are important sub cellular sites where mayor ROS production takes place [28,29]. This occurs from stimulus induced activation of membrane-bound enzymes systems like the mitochondrial electron transport chain (ETC) or NADPH oxidase complex [18]. If an overproduction of reactive species exists, mitochondrial dysfunction develops, increasing the leakage of electrons to form more superoxide radicals and therefore resulting in a vicious cycle of oxidative stress and tissue damage [19,24]. LPO is known to be the main cause of mitochondrial membrane irreversible impairment and damage, being the Fenton reaction one of the mechanisms involved in this process [24].

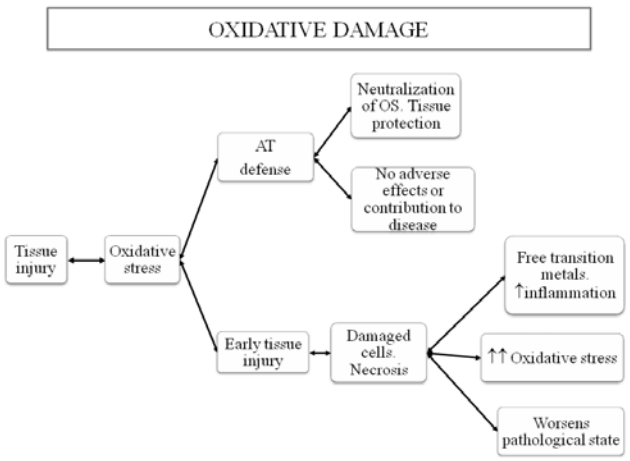
Due to the fact that all human tissues use oxygen, there is always a basal level of oxidative stress to DNA [21]. It seems that mtDNA is more susceptible to a ROS attack than nuclear DNA because the first one doesn't have structural proteins and it's attached to the inner mitochondrial membrane near the site of ROS generation, making it an easy target for mutation as a result of oxidative damage [24]. This mtDNA attack can result of DNA strand breaks and base oxidations as the most abundant alterations. Since its repair capacity is limited, the accumulation of mtDNA mutations has been reported to lead to mitochondrial dysfunction and is associated with a variety of cancers, neurodegenerative diseases, and aging [16,18,24,30].

Melatonin (explained later in this paper) has an important role in preventing mtDNA damage and thus mitochondrial dysfunction due to its cytoprotective characteristics as a potent antioxidant and its ability to increase mtDNA expression, promoting anti-aging properties [30]. Cellular's membrane damage consists of a decrease in the mitochondrial membrane potential, making it easier for phospholipids to exchange between the two halves of cell's bilayer and hence increasing the inner membrane permeability [24]. This leads to leakage of substances that usually do not cross to the extracellular space (i.e. K^{+}, Ca^{2+}) causing swelling, loss of the matrix components, damage of protein's membrane, inactivating receptors, enzymes, and ion channels, and an overall lost of membrane integrity [21,24]. Also, prostaglandin synthesis is strongly related to LPO, because low levels of peroxides accelerate cyclooxygenase action on PUFA [21].

In late stages of tissue injury, the necrotic death of some cells spreads damage to others, releasing more transition metals, exacerbating the oxidative damage and triggering the inflammatory cascade (Figure 1) depicts this vicious cycle in an explicatory diagram. Evidence shows that excessive inflammation and mitochondrial dysfunction contributes to age related diseases such as type 2 diabetes (T2DM), atherosclerosis, cardiovascular diseases, cancer, ageing, amongst others [18,19,24,27].

Antioxidants, role in redox homeostasis

Halliwell [22] defines an antioxidant (AT) as any substance that delays, prevents or removes oxidative damage to a target molecule. The defense against FRs overproduction involve preventive and repair mechanisms, and a proper antioxidant defense. They can be categorized into two groups: the enzymatic and the non enzymatic AT.



Abbreviations: AT: Antioxidant; OS: Oxidative stress

Figure 1: Illustrative flow chart that represents optimal antioxidant defense and cytoprotection on the upper side, versus the lack of antioxidant defense in oxidative stress and subsequent tissue injury in the lower side; and how this is related with necrosis, inflammation and increased oxidative stress, entering in a vicious cycle.

The first group is formed by superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) [16].

The second group includes nutritional AT such as ascorbic acid (Vitamin C), α-tocopherol (Vitamin E), polyphenols (flavonoids and phenolic acids), carotenoids, and glutathione (GSH) [16]. Also, the hormone melatonin, a potent antioxidant and antiinflamatory [31], further discussed herein.

Their role as a protector against intracellular oxidative stress, or "redox buffering", prevents oxidative damage and maintains the physiological redox homeostasis, membrane integrity and cellular well function. An excess of AT will also suppose an alteration to the pro oxidant-antioxidant balance favoring the AT side, affecting the basal oxidative stress level involved in many physiological functions, losing their defensive character and acquiring a cytotoxic modality. Table 1 presents a summary of some of the mayor enzymatic and non enzymatic AT, their function as defensive mechanisms and their cytotoxic effects in humans at high doses. Table 2 shows mayor biomarkers of oxidative stress in clinical assays. Nevertheless, there is still inconsistency in these investigations due to variability of study designs and methodology [18], for more studies are needed to determine the proper dose of AT so to maintain redox homeostasis. In Halliwell's 2009 review on free radicals [19], the author states that a paradox exists where the FRs are bad and therefore all antioxidants must be good and safe. But, as discussed here and elsewhere, reactive species are needed for some physiologic reactions; whereas an excess AT activity can also lead to oxidative stress (Table 1), and consequently can't be considered safe at high doses. Therefore, FRs and AT are not good nor bad, they are needed for keeping redox homeostasis, necessary for cellular integrity.

Recently, antioxidant investigations have turned their focus towards melatonin. This methoxy derivate of serotonin molecule, extracted and isolated from the pineal gland during the late 1950's, has been studied to determine its function as an antioxidant, as well as its effect on preventing cellular damage, along with others, during pregnancy for protection of placenta and fetus [31,32]. Chemically known as N-acetyl-5-methoxytryptamine, it is an endogenous indoleamine secreted nocturnally by the pineal gland in vertebrates; involved in regulation of the circadian rhythms [32,33]. It has proved to be a potent direct antioxidant, scavenging both oxygen and nitrogen species, and thus protecting all major molecules from free radical-mediated damage [31,33-41]. This is mainly attributable to its amphiphilic characteristic that allows it to enter mitochondria at time and dose dependant [30,42]. Due to this cytoprotector effect, it prevents LPO mediated by OH., and increases antioxidant activity by stimulation of AT enzymes (CuZnSOD, CuMgSOD and GPx) [32,43]. Furthermore, during the scavenging process, melatonin produces metabolites that have a potent antioxidant activity on their own: cyclic 3-hydroxymelatonin (c-3OHM) and N1-acetyl-N2-formyl-5-methoxykynyuramine (AFMK), forming a possible antioxidant cascade that still needs confirmation [31,32].

In fetus, this indoleamine scavenges ROS/RNS protecting it against oxidative damage, increases antioxidant enzymes, reduces cytokine toxicity [31] and lowers the risk of developing intrauterine growth restriction (IUGR) [33]. In placenta, melatonin also increases AT enzymes, protects against ischemia, and reduces severity of preeclampsia (PE) by improving redox homeostasis [32]. Evidence also shows that even at low doses, melatonin is more efficient than other well known AT (Vit. C, Vit. E) under specific conditions and experiments. Reiter et al. (2009) [31] present a well extended review of the effects of melatonin as a FR scavenger and its role on oxidative stress.

Due to melatonin's cytoprotective characteristics, it could be a good treatment approach to fight oxidative damage in some degenerative diseases and in complicated pregnancies with the presence of obesity or/and gestational diabetes mellitus (GDM). More research between melatonin and its use in physiological or pharmacological doses is needed to improve management, mainly in complicated pregnancies due to oxidative damage. To reduce oxidative damage, the ultimate antioxidant's activity, at a proper dosage, should not reach a cytotoxic effect, and must protect mitochondria, where the RON/RNS production takes place, without disturbance of the basal redox homeostasis, and maintaining membrane integrity [42].

Obesity, linking oxidative stress and inflammation

Obesity is defined as a chronic imbalance where energy intake exceeds energy expenditure, resulting in fat accumulation and weight gain [44]. Overnutrition from high calorie and fatty diets induces lipo- and glucotoxicity to the organism, increasing oxidative stress due to mitochondrial dysfunction with ROS overproduction, triggering the proinflammatory cascade and potentiating tissue damage [45-47]. For example, it has been demonstrated that excess free fatty acids (FFA) induce nitrosative damage in pancreatic islets and thus promote β-cell dysfunction [48], associated to the pathogenesis of T2DM. In addition, obesity is also a state of chronic inflammation [49,50] caused not only by an altered production of proinflammatory markers (tumoral necrosis factor α, interleukin-6, c-reactive protein) from white adipose tissue (WAT) due to increased fat accumulation; but also increased oxidative damage that enhances inflammation due to lipo- and glucotoxicity at a cellular level [49,51]. Therefore, it is clear that oxidative stress and inflammation coexists in obesity and that they should be ameliorated to prevent adverse outcomes, with promotion of healthy lifestyles that prevention of fat accumulation in WAT [52], mainly during critical stages of growth and development, such as pregnancy (Figure 2).

Role of oxidative stress in pregnancy and fetal outcomes

Non pathological pregnancies: At onset pregnancy, healthy

women undergo through mayor physiological changes that guarantee growth and development of the fetus as well as preparation for delivery, including an increase in plasma volume, creation of a thrombophilic state, increase in insulin resistance and immunosuppression [53]. Pregnancy per se is a condition of increased oxidative stress, compared to non-pregnant women, due to the high metabolic demand and elevated requirements of oxygen that contributes to ROS generation by placenta's mitochondria, along with cytokine production in a pro inflammatory state [32,33]. Placenta is believed to be a major source of free radicals and LPO production, leading to systemic oxidative stress at onset of pregnancy and during delivery [32,33]. Usually, healthy young women cope with these physiologic changes which are controlled by an increase in antioxidant activity [mostly SOD and CAT, see Table 1 as gestation advances without reporting adverse outcomes [33,53].

Pathological pregnancies, programming obesity: Consequently, if an insufficient antioxidant defense is present, it may lead to an increased oxidative damage; changes that can be related to insulin resistance or pathological circumstances such as obesity, gestational diabetic mellitus (GDM), and thus adverse outcomes in child like macrosomia or intrauterine growth restriction (IUGR) [33,43,54,55]. In addition, insulin resistance (impaired ability of insulin to lower blood glucose levels), is suspected to be an early metabolic abnormality that precedes the development of T2DM [56].

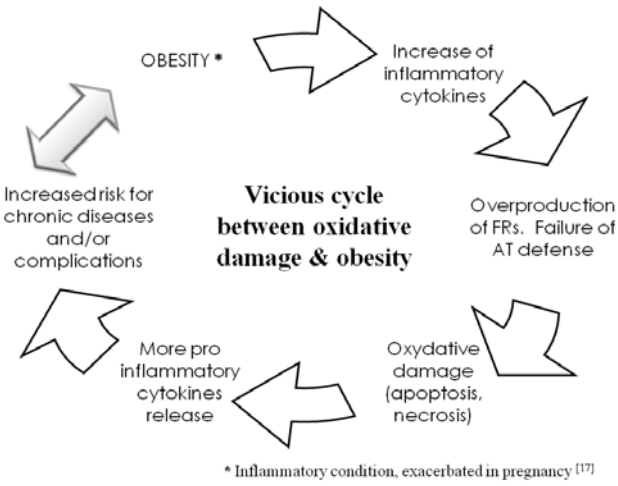
In women with a pregestational overweight or with a predisposition to develop degenerative diseases, these changes may have a strong influence in the fetal metabolic programming of obesity. This concept is referred as a permanent change, related to a particular function, through adaptations at a cellular, molecular and biochemical level, which results are due to some event occurred during critical periods in early development, strictly related to metabolic disorders and appetite during adulthood [57-59].

Epidemiological studies have shown a clear association between excess maternal pregravid weight and adverse birth outcomes [55,56,60]. Future mothers with high body mass index (BMI ≥ 25-29.9 kg/m^2 in overweight, and ≥ 30 kg/m^2 in obese women) have higher risks of developing GDM, pregnancy induced hypertension and PE, have more cesarean sections (C-section), prolonged labor, postpartum anemia, birth defects (congenital heart diseases, neural tube defects) and macrosomic offspring (>4500g) or large for gestational age (LGA) [33,60-62]. Also, low birth weight and IUGR, as well as macrosomia, have been associated with metabolic syndrome in adulthood, because of early metabolic programming of obesity [63]. Since pregnancy is a state of increased physiological oxidative stress, and high pregestational body weight (especially in those with android fat distribution) should exacerbate oxidative damage according to the evidence presented above; then overproduction of free radicals should be assessed in these subjects. To illustrate these statements (Figure 2) depicts the vicious cycle of oxidative damage and obesity; whereas (Figure 3) demonstrates the differences between increased physiological oxidative stress status in normal-weight pregnant women versus pathological oxidative stress status in overweight- pregnant women, as well as the effects on the newborn.

In Tozuka's [1] murine model, where dams fed on a high fat diet (HFD) developed obesity and then were mated, results show malondialdehyde (MDA) accumulation in hippocampal neural progenitor cells of HFD offspring, postulating that offspring might be vulnerable to peroxidative damage and thus influence in neurogenesis and metabolic programming of obesity.

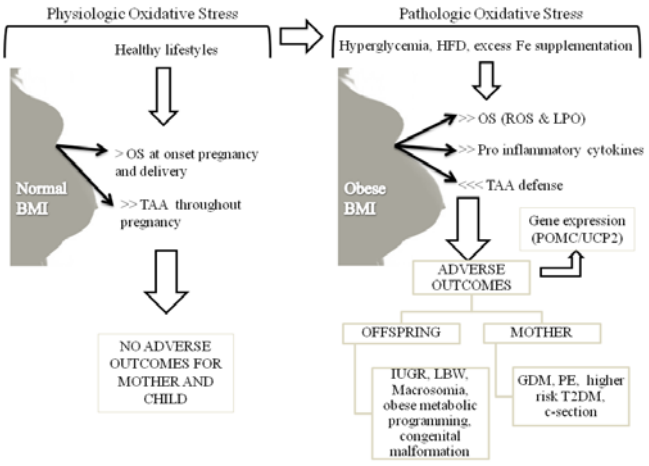
Since pregnancy is a state of physiological oxidative stress, and pregestational overweight (especially in those with android fat distribution) should exacerbate oxidative damage according to the evidence presented here and elsewhere [45,49,64,65]; then oxidative damage may be involved in the progression and/or pathogenesis of GDM [65] as well as other degenerative diseases.

As a result, assessment and recognition of oxidative damage and presence of degenerative diseases during pregnancy comes to be of



Abbreviations: RS: Radical Species; AT: Antioxidant

Figure 2: Illustrative diagram that shows the interaction between obesity and reactive oxygen species, how they can enter in a vicious cycle enhancing inflammation, apoptosis and worsen degenerative diseases if present.



Abbreviations: BMI: Body Mass Index; OS: Oxidative Stress; TAA: Total Antioxidant Activity; HFD: High Fatty Diet; Fe: Iron; ROS: Reactive Oxygen Species; LPO: Lipid Peroxidation; IUGR: IntraUterine Growth Restriction; GDM: Gestational Diabetes Mellitus; PE: PreEclampsia; T2DM: Type 2 Diabetes Mellitus

Figure 3: Summary of the hypothesis presented in this minireview, whereas obese pregnant women would show an increase of reactive species, leading to a pathologic oxidative stress status versus de normal-weight pregnant women; alterations which have also been associated with higher risks of adverse outcomes in mother and metabolic programming of child.

high relevance, with continuous screening and proper interventions that guarantee improvement on health outcomes for mother and child. Table 3 and Table 4 (Data included as supplementary) present oxidative stress increased markers in pregnant women at different pre gravid weights (normal and obese), presence of hyperglycemia, and its association with other physiopathology conditions with possible birth outcomes.

Melatonin as potential treatment in high risk pregnancies

Several studies, both in animals and humans, have measured OS in plasma, placenta and cord blood, determining that there's an increased level of biomarkers of OS and decrease level in total antioxidant activity, mostly seen in pregnancies where hyperglycemia is already present, as well as in obese pregnant women, compared to control normal-weight groups; evidence presented in Table 3 and Table 4 (Data included as supplementary).

Hyperglycemia is a widely known cause of increased oxidative damage with a teratogenic effect [66,67]. These metabolic alterations have also been linked to short and long term adverse outcomes in offspring, from IUGR and congenital malformations, to development of metabolic syndrome during adolescence and adulthood.

With all the information and investigations presented, it could be hypothesized that obese non pregnant women have an increased oxidative damage versus lean woman, and that this state can be worsen if hyperglycemia is present. Since pregnancy *per se* has a physiologic increase in oxidative stress, then obese pregnant women or pregnancies with hyperglycemia would present much more adversities due to the complications, entering into the vicious cycle of oxidative damage, inflammation and possible placental and cellular dysfunction. Whether these alterations on redox homeostasis are cause or consequence of the disease, is still unknown; it can only be guessed that oxidative damage has an important role in programming obesity and is strongly linked to these changes, but more investigation is needed to determine whether improvement on the prooxidant-antioxidant balance in pregnancy may prevent or treat such adverse outcomes.

Some recent data suggest melatonin's positive effects as an antioxidant and antiinflammatory therapy in neonates [33], cancer [68-70], neurodegenerative diseases [71,72], and ageing [73,74], amongst others. Thus, this hormone might have an important role in ameliorating oxidative damage and proinflammatory state present in high risk pregnancies. As reviewed in [52] and presented by Agil et al (2011) [75], melatonin also plays an important role in body weight and adiposity, associated to its circadian rhythm control. Chronodisruption, or alterations in endogenous melatonin secretion by pineal gland, has been related to disturbance in glucose and lipid homeostasis, increased weight gain and body fat mass [52,76]. Therefore, its function in improving metabolic alterations associated to obesity can also be used in obese and diabetic pregnancies.

Type of AT	Name	Role in redox homeostasis	Prooxidant role (cytotoxic effect)
Enzymatic	SOD	Catalyzes dismutation of superoxide radical to form oxygen and hydrogen peroxide	None observed so far.
	GPx and GSH	Scavenges hydroxyl radical and prevents LPO cellular damage, with GSH as electron donor. Regenerates Vit C and E to their active form.	None observed so far.
Non enzymatic	α-tocopherol (Vit. E)	Free radical chain-breaking molecule inhibiting LPO by capturing electrons and converting into α-tocopheroxyl.	In clinical studies massive doses (3000 mg/day) have not been found toxic.
	Ascorbic acid (Vit. C)	Scavenges ROS, protecting of mtDNA. It also restores oxidized α-tocopheroxyl to its AT form.	Mega doses: renal stone, iron overload, destruction of B12 in the gut.
	Polyphenols	Scavenges FR, reduces hydroperoxides.	More clinical studies needed.
	Melatonin	FR scavenger ($OH^{\cdot}$), prevents LPO. Its metabolites (c-3OHM and AFMK) also have AT action. Protects and stimulates enzymatic AT.	No toxicity or adverse effects have been found at high doses in pregnant rats.

SOD: superoxide dismutase, **GPx:** Glutathione peroxidase, **GSH**: Glutathione, **AT:** Antioxidant, **FR**: free radicals, **LPO:** lipid peroxidation.

Table 1: Summary of antioxidants (AT) and their role in redox homeostasis and oxidative stress.

Biomarkers	Name	Source of sample to assay biomarker
DNA oxidation and damage	8-hydroxydeoxyguanosine (8-OHdG), purine residue of DNA damaged by ROS	Urine (marker of total systemic oxidative stress in vivo)
Lipid peroxidation	8-isoprostane (8-IP) 8-iso-prostaglandin F2α (8-iso-PGF2). Prostaglandin-like compounds formed by FR- catalyzed peroxidation of AA.	Plasma and urine
	Malondialdehyde (MDA), product of UFA peroxidation	Serum, plasma, blood erythrocytes and urine
Protein damage	Protein carbonyl groups, that result from free radical induced protein oxidation	Blood erythrocytes

arachidonic acid (AA); free radicals (FR); unsaturated fatty acids (UFA)

Table 2: Biomarkers of oxidative stress and the source of sample to assay.

	Pre gestational weight (BMI=kg/m²)		
	Normal (18.6 – 24.9 kg/m²)	***Overweight (25 – 29.9 kg/m²)***	***Obese (≥30 kg/m²)***
Adaptation due to oxidative stress status	Normal physiological OS in mother due to an increase in plasma volume, insulin resistance, inmuno-suppression and thrombophilic state.	Same changes as in normal pre gestational weight mothers, with increased insulin resistance, possible oral glucose intolerance, increase in pro inflammatory cytokines and oxidative damage (pathologic oxidative stress).	Same changes as in pregestational normal-weight mother; plus possible oral glucose intolerance, increase in pro inflammatory cytokines, oxidative damage (pathologic oxidative stress), and biomarkers of metabolic syndrome. Increased risk of IUGR, GDM and T2DM, PE, AHT, UTI, CAD, amongst others.

preeclampsia (PE); intrauterine growth restriction (IUGR); gestational diabetes mellitus (GDM); type two diabetes mellitus (T2DM); coronary artery disease (CAD); arterial hypertension (AHT); urinary tract infection (UTI)

Table 3: Oxidative stress status according to pregravid weight in pregnant women, compared to non pregnant women, and risk of degenerative diseases.

Since hyperglycemia and alterations in the lipid profile have an important role in lipo- and glucotoxicity and increase risk of metabolic diseases during and after pregnancy, as well as possible early obese programming in offspring; then pharmacological treatment with melatonin should be profoundly investigated in longitudinal clinical trials during pregnancy so later it can be recommended as clinical use.

To date, and to the author's knowledge, no study has been published where melatonin is used as a drug to prevent or treat hyperglycemia in gestational diabetic pregnancies, as well as diminishing oxidative damage in obese pregnant women. However, various authors have reported the role of melatonin in animal and human models where it improves these parameters, which consequently has an impact in diminishing oxidative damage, including an antiinflammatory response, as well as improving weight gain.

Melatonin insufficiency has showed to increase body weight in pinealectomized rats [77]; whereas in craniopharyngioma child patients, its nocturnal secretion was decreased causing daytime sleepiness and obesity; reinforcing the role of this indoleamine in weight control [78]. In animal models fed on a high fat diet (HFD), melatonin supplementation managed to decrease body weight in rats [77,79,80] and rabbits [81]. Similar results were reported by [82], where a selective melatonin agonist was used in spontaneously hypertensive rats, and in the young male Zucker diabetic fatty (ZDF) rat model [75].

As to improving lipid metabolism, Tamura et al (2008) [83] recently show the positive effects of melatonin supplementation in peri- and postmenopausal women by increasing HDL-cholesterol plasmatic levels; while authors [84] also show a reduction of LDL-cholesterol in the same target group. Conversely, in this study [85], authors did not find melatonin having any effects on HDL and LDL cholesterol levels on normolipidemic postmenopausal women.

Some researchers have found similar effects on diminishing total-cholesterol absorption in rats [86] and in rabbits [87] fed on HFD by improving serum lipid levels and reducing metabolic pathologies associated to the HFD intake. Recently, Agil et al (2011) [75] show improvements on lipid profile using the Zucker diabetic fatty (ZDF) rat model, with increases of HDL cholesterol and reductions in LDL cholesterol and triglycerides levels. In T2DM poorly controlled patients, melatonin treatment in combination with zinc, also improved lipid profile by decreasing the susceptibility of lipoproteins to oxidation damage [88]. Recently, melatonin also showed its cytoprotective behavior by improving cardiovascular physiology and heart function in murine models [89]. According to these investigations, and given the role of lipids in LPO; melatonin not only scavenges free radicals, but also improves lipid plasma levels as discussed above, decreasing directly the risk of lipotoxicity and oxidative damage.

Equally, various investigations have also reported the role of melatonin on glycaemic metabolism in both animal and human models. Previously, it was mentioned that hyperglycemia has an important role in the generation of FRs and thus oxidative damage in pregnancy. In Peschke's mini review [40], a general agreement exists where melatonin is essential for homeostasis and regulation of both glucose metabolism and insulin secretion from the pancreatic β–cell by stimulating intracellular glucose transport to skeletal muscle cells; effect also seen in bats [90]. Other studies report this hormone's capacity to decrease hyperglycemia and prevent insulin resistance in induced HFD animal models [91-94]. Agil et al (2011) [95] report that in the young male ZDF rat model, oral melatonin has an antidiabetic effect by improving insulin secretion and action, β-cell function, as well as by producing an antiatherogenic effect ameliorating the leptin/adiponectin ratio. This clinical trial [76] reported a strong interaction between melatonin, insulin and lipid profile in metabolic syndrome patients. Nishida's review [96] and Wolden-Hanson's experiment on rats [79] are also in accordance with these investigations, affirming that melatonin has an important role in diabetic rats and subjects, by helping to prevent oxidative stress, reduce hyperlipidemia and hyperinsulinemia, decreasing intraabdominal adiposity, and thus improving parameters of the metabolic syndrome.

Regarding its toxicity, there seems to be a common agreement between the scientific community that melatonin is a nontoxic molecule, safe at pharmacological doses, with no side effects reported in both animals including pregnant rats [97], and human studies [32,33,35,98]. Even so, [99] report that high doses of melatonin on hypercholesterolemic mice fed with a HFD increases the surface of atherosclerotic lesions in the proximal aorta, and therefore advice caution regarding melatonin supplementation in hypercholesterolemic patients and more investigations to determine its toxicity.

Melatonin has a direct antioxidant activity and is a potent cytoprotector preventing lipo- and glico toxicity [45], attenuates hyperglycemia, dyslipidemia and overweight by central action [52,75,95], may have anti-aging properties due to its capability to protect mtDNA and ameliorate mitochondrial dysfunction [30], and no reports seem to show toxic effects or side effects, and has been widely analyzed in human trials [100]. Therefore it could be proposed as a pharmacological treatment to improve oxidative damage in obese and/or diabetic pregnancies, and to reduce risk of programming obesity in fetus.

Possible melatonin pathways to improve metabolic parameters, implications of melatonin as an epigenetic regulator of POMC

So far, a possible relationship between increased oxidative stress in obese and/or diabetic pregnancies and adverse outcomes on mother and fetus, including early obesity programming has been established; as well as melatonin's probable use as a therapeutic drug that can ameliorate oxidative damage targeted to these subjects. Due to this indolamin's cytoprotective effect on mitochondria, then one could speculate that it scavenges ROS generation in hypothalamic neurons' mitochondria that are in charge of controlling energy metabolism.

Animal and human model investigations have shown various pathways associated to the early programming of obesity; including alterations in gene expression during critical periods of life (fetal/neonatal growth and development). Up till now, various susceptible genes have been linked to obesity pre-programming [101,102]. Of these, the neurons from the arched nucleus producers of pro-opiomelanocortin (POMC) have received special attention since they participate in the regulation of food intake and body weight [103].

Various researchers have linked POMC gene expression with an important role in early obesity programming, discussed herein. Pro-opiomelanocortin, also known as anorexigenic neurohormone, is found in the arched nucleus of the hypothalamus [104,105]; is a multifunctional protein precursor submitted to specific cellular processes, producing a big quantity of bioactive peptides, including the α-melanocyte stimulating hormone (α-MSH) and adrenocorticotropina hormone (ACTH) [103,106]. α-MSH release by POMC neurons acts on central mechanisms to diminish food intake and increase metabolic activity. Also, it has been reported that leptin and glucose receptors,

both implicated in regulation of energy metabolism, act on POMC [105,107]. The genetic deficit of POMC can lead to alterations in ACTH secretion induced by hypocortisolemia, provoking hiperfagia that results in severe obesity [106].

According to animal investigations, a protein and calorie restriction neonatal diet in offspring [59,104,108], or maternal malnutrition during pregnancy [109-111], can lead to epigenetic alterations of POMC; which can be associated to an early programming of obesity [112]. Likewise, these authors [105] report in their research with transgenic rats that glucose susceptibility by the POMC neurons has an important role in the control of glucose homeostasis, which is lost in an obesity stage induced by high fatty diets.

The fact that POMC neurons also exhibit a circadian pattern of rhythmic activity, a relationship between these and melatonin may exist; with the last one being able to modulate its gene expression resulting in possible decrease in leptin levels [113]. In addition, the capacity of melatonin to scavenge ROS overproduction in POMC's mitochondria might prevent oxidative damage, protecting these neurons from epigenetic changes during pregnancies with presence of excessive pregestational weight or hyperglycemia. Further investigations are needed in this field during critical stages of life so to determine if melatonin preserves POMC neurons and its capability to control energy metabolism.

Therefore, nutrition during critical periods of development constitutes a critical environmental factor that marks metabolic programming for both mother and child. If diets were to be deficient or excessive in quantity or quality, then they might induce a greater risk of metabolic alterations in adulthood, such as besity, diabetes or metabolic syndrome (Table 4 Data included as supplementary), related to increased oxidative stress.

Future Perspectives

Numerous actions are being applied throughout the world at many levels to fight obesity and diabetes, from community programs to public health strategies; but the question of how the obesity vicious cycle can be broken remains unanswered. The best bet would be to treat maternal and pre-maternal excess weight and hyperglycemia, prior to metabolic programming of fetus; consisting in dietetic treatment and promotion of healthy lifestyles, managing glucose concentrations in diabetic pregnancies guided by a health professionals working in a multidisciplinary team. Treatment should also recommend a rich antioxidant diet with natural food sources and increased physical activity level to reduce oxidative damage, improve glucose tolerance and prevent insulin resistance [114]. Also, recommend avoidance of a high saturated fatty acid diet [1,66,115,116] that may induce oxidative stress by lipid peroxidation and lipotoxicity.

As to melatonin, increasing dietary intake should be encouraged, although more investigation is needed regarding dietary intake recommendations that may increase serum levels. Actually, relevant quantities of melatonin have been found in roots, leaves, fruits and seeds [117]. With these interventions it could be expected, and should be aimed, that healthier women give birth to healthier children that would become a low risk adult for chronic diseases.

The novel findings on melatonin's cytoprotective capacity may lead to a new target to prevent or treat oxidative damage, mainly in high risk pregnancies where obesity and hyperglycemia coexist, considering its benign safety profile and its probable role as epigenetic regulator, including fetal early obesity programming. Maternal melatonin easily transfers to fetal circulation near term, and thus neonatal melatonin levels will depend mainly from maternal endogenous production [118]. Recommendations of melatonin's administration should be focused in a nocturnal intake in order to be consistent with its circadian rhythm, and should begin at the 24th week of pregnancy since it is when this indoleamine starts to rise in pregnant women [118,119]. This considering that newborns from diabetic or obese mothers are prone to increased oxidative damage [33], which could also be related to early metabolic programming of obesity, by using melatonin as an epigenetic regulator [117].

Consequently, the need for more longitudinal studies or randomized clinical trials that measure oxidative damage throughout all pregnancy and early infancy arises, considering presence of excessive pregestational weight and of hyperglycemia; as well as the variety of biomarkers used to measure oxidative stress, including the novel melatonin as antioxidant. In addition, the study of POMC gene expression, probably enhanced by melatonin, could be another interesting pathway to minimize oxidative damage in obese and/or diabetic pregnant woman and thus prevent adverse outcomes on mother and early obese metabolic programming on fetus.

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