MECHANISMS IN ENDOCRINOLOGY

Nutrition as a mediator of oxidative stress in metabolic and reproductive disorders in women

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Abstract

Nutrition can generate oxidative stress and trigger a cascade of molecular events that can disrupt oxidative and hormonal balance. Nutrient ingestion promotes a major inflammatory and oxidative response at the cellular level in the postprandial state, altering the metabolic state of tissues. A domino of unfavorable metabolic changes is orchestrated in the main metabolic organs, including adipose tissue, skeletal muscle, liver and pancreas, where subclinical inflammation, endothelial dysfunction, mitochondrial deregulation and impaired insulin response and secretion take place. Simultaneously, in reproductive tissues, nutrition-induced oxidative stress can potentially violate delicate oxidative balance that is mandatory to secure normal reproductive function. Taken all the above into account, nutrition and its accompanying postprandial oxidative stress, in the unique context of female hormonal background, can potentially compromise normal metabolic and reproductive functions in women and may act as an active mediator of various metabolic and reproductive disorders.

Introduction

Oxidative metabolism and redox homeostasis have been gradually highlighted as an integral part of aerobic life (1). Living organisms cannot exist without oxygen; yet under unfavorable cellular conditions, oxygen derivatives can interrupt oxidative equilibrium; damage proteins, lipids and nucleic acids; and compromise cell viability (2). Hence, oxidative stress was introduced to define the imbalance between excessive formation of oxidants in the presence of limited antioxidant defenses in the human body (3).

There is an increasing body of evidence showing that oxidative stress lies in the pathophysiological core of a plethora of human diseases (4, 5, 6). However, even under physiological conditions, normal functions of human body, such as nutrition, can potentially generate oxidative stress. Macronutrients can be inflammatory and possibly

Invited Author’s profile

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Elements of fundamentals of oxidative metabolism

There are two main classes of free radicals or oxidants: reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS derive from molecular oxygen, formed upon incomplete reaction of oxygen, including superoxide anion \( \left( O_2^- \right) \), hydroxyl radical \( \left( \cdot OH \right) \) and singlet oxygen and hydrogen peroxide \( \left( H_2O_2 \right) \) (11). This activation takes place via different cellular processes (Fig. 1) (12). However, mitochondria are considered to be the principal source of ROS. Specifically, in the mitochondrial electron transport chain (ETC), there is a tendency for an electron to directly pass to oxygen, generating eventually superoxide \( \left( O_2^- \right) \) (13).

RNS are a family of chemical compounds that derive from nitric oxide (NO) (14). Physiologically, NO is synthesized from \( \alpha \)-arginine, via the catalytic action of nitric oxide synthase (NOS) and under the presence of catalytic cofactors, tetrahydrobiopterin (BH4), flavin adenine dinucleotide and flavin mononucleotide (FMN) (15). Under certain stimuli, NO reacts with superoxide \( \left( \cdot O_2^- \right) \) generating peroxynitrite \( \left( ONOO^- \right) \), which is believed to be one of the most toxic RNS produced in human body and can further promote the production of other forms of RNS, such as nitrogen dioxide \( \left( \cdot NO_2 \right) \) and dinitrogen trioxide \( \left( N_2O_3 \right) \) (16).

In addition to the above mentioned pro-oxidants, other molecules that have also been acknowledged to share truly pro-oxidant and inflammatory properties are AGEs. AGEs, or glycoxidins, constitute a heterogeneous group of more than 20 different compounds, derived from endogenous nonenzymatic glycation of macromolecules, as well as from absorbed exogenous sources (17). Upon their formation, AGEs promote ROS and RNS formation, via multiple mechanisms (18). Binding of AGEs to their multiligand receptor for advanced glycation end products (RAGE) activates NF-\( \kappa \)B, which in turn leads to increased ROS generation, as well as to the activation of NADPH oxidase (19, 20).

Antioxidants are the opposing force of human body to maintain oxidative equilibrium (Fig. 2) (21). They can be divided into two major categories: enzymatic and nonenzymatic. Enzymatic antioxidants constitute innate, key enzymes that can detoxify excessive ROS and RNS, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) (22), whereas nonenzymatic antioxidants are exogenous and endogenous molecules, such as glutathione, thioredoxin, vitamin C, vitamin A, vitamin E, selenium (Se) and zinc (Zn), used to terminate pro-oxidants (13, 23).

When overproduction of free radicals cannot be compensated by the powerful antioxidant defense system of the body, oxidative stress dominates (24) and...
ROS initiate multiple molecular pathways (12, 25, 26). This active implication of ROS in multiple molecular pathways has led scientific society to investigate the role of oxidative stress not only in the pathophysiology of a variety of diseases (5, 27, 28, 29, 30, 31) but also in normal physiological functions of human body, such as nutrition. Since the establishment of the bidirectional association between caloric intake and low-grade inflammation (32), a crucial query emerged whether macronutrients themselves can be inflammatory and pro-oxidant stimuli for the human body that can postprandially trigger oxidative stress and alter body’s homeostasis (33).

**Nutrition is a major modulator of oxidative stress**

**Nutrition triggers oxidative stress early in life**

Since the establishment of the ‘Developmental origins of health and diseases’ hypothesis, which postulates that early life development is critically sensitive to environmental stimuli, there is an increasing share of literature focusing on how environmental factors acting during early human development can affect the risk for health and disease.

Among environmental factors, nutrition as a potent promoter of these intrauterine epigenetic modifications has been extensively studied (34). Specifically, undernutrition in utero and low birth weight, combined with early catch-up growth during infancy has been linked to increased risk for obesity, insulin resistance, cardiovascular disease and reproductive dysregulation in adulthood (35, 36, 37). Likewise, offspring raised in the context of a prenatally rich nutritional environment are at an increased risk for cardiometabolic disorders and compromised fertility later in life (38, 39).

Oxidative stress has been proposed as a potential mediator of nutrition-induced epigenetic changes through various experimental models (40). Maternal malnutrition, obesity or obesogenic maternal diet during gestation, but not during postweaning period (41), was associated with increased oxidative stress markers and impaired antioxidant capacity in the offspring, making them vulnerable to diabetogenic effects (42, 43). Simultaneously, antioxidant supplementation was accompanied by a significant attenuation of adiposity in their offspring (44).

Currently, the majority of evidence regarding the domain of developmental programming originates from experimental models, and there is a long way until definitive conclusions be established. However, nutrition during the critical periods of prenatal and perinatal development can induce epigenetic changes, via different pathways, including generation of oxidative stress, an evolving risk factor for metabolic as well as reproductive disorders in adulthood.

**Nutrition and oxidative stress at the cellular level**

The initial observation by Mohanty et al. demonstrating that a macronutrient induces inflammation and ROS generation by polymorphonuclear (PMN) and mononuclear (MNC) leukocytes was after glucose intake by normal subjects (45). Analogous findings for lipid and protein intake were also published. Acute ingestion of saturated fat (cream) led to an increase in ROS generation by leukocytes, similar in magnitude to that of glucose ingestion but more prolonged and persistent, whereas protein (cysein) intake also increased oxidative ROS formation but to a much lesser extent in comparison with glucose and lipids (46). Furthermore, evaluating a real mixed meal in healthy subjects, acute...
Inflammatory changes were detected, with a decrease in IkBα and an increase in NF-κB binding, plasma CRP and the expression of inhibitory proteins IKKα and IKKβ, and p47phox subunit (47).

Therefore, a new term – dietary or nutritional or postprandial oxidative stress – has been introduced to describe the postprandial state of imbalance between the pro-oxidant load and the antioxidant defense as a consequence of excess oxidative load or of inadequate supply of antioxidant nutrients (8). Postprandially, ROS formation and generation, originating from leukocytes and mitochondria, can be modulated by several coexisting factors (Fig. 3).

The amount of caloric intake is a decisive factor affecting the intensity of the postprandial oxidative stress. Excessive amount of high-calorie food results in abnormal surges in blood glucose, triglycerides and free fatty acids (FFA) in blood circulation. These ample concentrations of glucose and FFA outpace the total capacity of mitochondria for oxidative phosphorylation, eventually leading to increased transfer of single electrons to molecular oxygen. As a result, more and more superoxide anions enter the circulation (10, 48, 49). Apart from mitochondria, ROS generation by leukocytes is also affected by the caloric amount, as indicated by studies in which caloric restriction led to a respectable decrease in ROS generation by leukocytes, lipid peroxidation and protein carbonylation (50, 51, 52).

Furthermore, the type of micronutrients consumed is also catalytic in the amplitude of postprandial oxidative stress. As mentioned above, carbohydrate and lipid consumption evokes equal oxidative responses by leukocytes, except for the fact that the latter evokes a more prolonged one. Regarding lipids, the type of fat consumed may have a role in the immediate postprandial inflammation, as saturated fats (SFA) have been closely linked to CVD, whereas n-3 polyunsaturated fats (PUFA) are known to exert an anti-inflammatory effect (53, 54). However, scientific data are contradictory and have failed to prove clear beneficial effect of the consumption of PUFA-rich meals on postprandial plasma inflammatory cytokines or a detrimental effect of SFA in an acute feeding scenario (55, 56). Simultaneously, regarding carbohydrates, differences in postprandial oxidative stress were reported in terms of glycemic index, as consumption of high glycemic index carbohydrates by healthy subjects resulted in a more avid activation of MNCs and increased concentration of NF-κB (57).

Consumption of antioxidant and anti-inflammatory nutrients can also influence the oxidative milieu in the postprandial state. For example, orange juice intake when combined with a high-fat, high-carbohydrate meal was shown to prevent the meal-induced oxidative and inflammatory stress in normal subjects, with a total inhibition of ROS generation and a decrease in proinflammatory gene expression (58). In a similar setting, red wine, which is established to have a protective effect against atherosclerosis and CVD, was also shown to prevent meal-induced oxidative stress and mitigate the postprandial increase in LDL susceptibility to oxidation (59, 60, 61).

Lifestyle characteristics of an individual, such as presence of obesity or physical inactivity, can also affect ROS generation in the postprandial state. Therefore,
as depicted in a study by Bloomer et al., obese subjects experience an exaggerated and more persistent oxidative stress in response to a high-fat meal in comparison with non-obese healthy individuals (62). Regarding exercise, contradictory data prevail in the literature concerning its effect in postprandial oxidative stress. Although exercise is considered as a powerful tool of upregulating endogenous antioxidant defenses, various researches have failed to display a beneficial effect of training status in the postprandial oxidative stress (63, 64, 65).

Finally, cooking methods can also have an aggravating impact on oxidative metabolism postprandially. Foods, high in protein and fat, cooked shortly under high temperature lead to formation of dietary AGEs (12). Uribarri et al. showed that a single oral challenge by AGEs (coke) resulted postprandially in acute endothelial dysfunction, as depicted by a significant decrease in flow-mediated dilatation both in healthy and in diabetic subjects (66). Dietary AGEs seem to have a negative impact on reproductive disturbed women, as well. In a study by our group in women with PCOS, it was shown that low-AGE diet in conjunction with 6-month administration of a lipase inhibitor (orlistat) led to a respectable improvement of their hormonal profile, independent of BMI changes (67).

Taken all the above into account, there is a large body of evidence indicating that nutrition induces major inflammatory and oxidative derangements in the postprandial state. Indeed, postprandial hyperglycemia and hyperlipidemia, or so-called postprandial dysmetabolism, are slowly gaining important attention as major risk factors in various diseases. Incessant accumulation of all these derangements during the continuous postprandial state that characterizes modern lifestyle may contribute to the pathophysiology of metabolic and reproductive disorders in women as well.

**Nutrition and oxidative stress at the metabolic tissues level**

Nutrient ingestion triggers a major inflammatory and oxidative response at the cellular level altering the metabolic status of the tissues. Postprandial oxidative stress, after carbohydrate, lipid and protein intake, orchestrates a domino of metabolic changes in different tissues including adipose tissue, skeletal muscle, liver and pancreatic β-cells. These active but metabolically disturbed tissues interacting with nutrients will further aggravate oxidative stress and ultimately initiate an endless vicious cycle (Fig. 4).

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**Figure 4**

Nutrition as mediator of oxidative stress at the metabolic tissues level (ER: endoplasmic reticulum, FoxO1: Forkhead box protein O1, IL-6: Interleukin 6, MCP-1: Monocyte chemoattractant protein-1, TLR4: Toll-like receptor 4, ETC: electron transport chain).

**Adipose tissue**

Adipose tissue is as an active endocrine organ with multiple metabolic and hormonal actions with a central role in the insulin-mediated glucose uptake, contributing to the metabolic balance of the human body (68).

Oxidative metabolism and ROS production are major players in adipose tissue function (69). There are different sources of intracellular ROS in adipocytes. First, although adipocytes are not considered pure energy-producing cells, ROS may derive from mitochondria and ETC substrate overload (70). In addition, various enzymes can promote ROS production in adipocytes, such as NADPH oxidase. NADPH oxidase 4 (NOX4) is the major isoform of the enzyme expressed in adipocytes and is increased in fat cells exposed to excess nutrient derivatives, such as glucose or palmitate (71). Silencing of NOX4 in 3T3-L1 adipocytes inhibits palmitate- and glucose-stimulated ROS generation underlying the importance of non-mitochondrial sources of ROS in adipocytes (72). Additionally, NOS appears to be a significant contributor to ROS generation. Endothelial NOS (eNOS) and inducible NOS (iNOS) are abundant in adipocytes and their expression was found to be higher in the white adipose tissue of obese patients compared with lean controls, suggesting that obesity is accompanied by an altered oxidative status that may possibly have an unfavorable impact on nutrient utilization postprandially (73).
ROS in adipose tissue seem to have a potential physiological role in its metabolic function. Early reports have highlighted that insulin may elicit H$_{2}$O$_{2}$ production in adipocytes (74). This transient H$_{2}$O$_{2}$ production amplifies insulin-signaling cascade, as it enhances translocation of GLUT transporters and glucose uptake, additionally promotes lipid synthesis and inhibits lipolysis (75, 76).

Following consumption of a meal, an inflammatory response takes place in the adipose tissue (77). This was first shown in a rat model by Magne et al., where rats fed with high-fat meal displayed an acute postprandial activation of inflammatory signaling in visceral adipose tissue (78). Similarly, in humans as shown by Travers et al., 6h after the consumption of a mixed meal by three different groups of normal-weight, overweight and obese subjects, a similar increase in IL-6 and MCP-1 was detected within adipose tissue, independent of the degree of adiposity (79). Furthermore, whether the specific quality and quantity of dietary fat alters postprandial inflammatory response in adipose tissue was addressed by different scientific groups, but data remain contradictory. On one hand, the LIPGENE study of 75 subjects with metabolic syndrome demonstrated that long-term consumption of a diet high in monounsaturated fat led to attenuated postprandial inflammatory response in adipose tissue compared with a saturated fat diet (80), whereas a study by Meneses et al. showed that individuals with metabolic syndrome exhibit an exacerbated postprandial adipose tissue inflammation, independent of the degree of adiposity (81). Apart from the direct activation of inflammatory pathways by nutrient ingestion, a high-fat diet may induce local inflammation in adipose tissue through the release of excessive FFAs. The effects of FFAs on inflammatory pathways are mediated via the Toll-like receptor (TLR-4), which further promotes macrophage accumulation in the adipose tissue and secretion of various cytokines (82).

Finally, oxidative stress can also be detected postprandially in the adipose tissue. In cultured adipocytes, elevated FFA resulted in increased oxidative stress, via NADPH oxidase activation, and oxidative stress led to a dysregulated secretion of adipokines, as shown by Furokawa et al., What's more, in the same study, increased ROS production accompanied by augmented expression of NADPH oxidase and decreased expression of antioxidative enzymes was observed in the adipose tissue of obese mice (83). Therefore, the nutrition-induced oxidative stress could possibly lead to an adverse local redox status that could interfere in the role of free radicals in adipose tissue (84).

Skeletal muscle

Skeletal muscle can be characterized as a traffic controller of the metabolic circulation. It accounts for about 80% of postprandial insulin-stimulated glucose disposal and represents a cardinal source of energy production (85). As a pure energy-producing organ, skeletal muscle is full of mitochondria that exert a regulatory role in energy homeostasis.

After nutrient intake, insulin promotes glucose uptake in skeletal muscle via GLUT4 transporters (86). This is a critical step in the body's metabolic pathways, as fuel utilization should be adjusted to fuel availability. The capacity of skeletal muscle to switch from predominantly lipid oxidation and high rates of fatty acid uptake during fasting conditions to the suppression of lipid oxidation and increased glucose uptake, oxidation and storage under insulin-stimulated conditions is known as metabolic flexibility. Inability to switch from lipid to carbohydrate use (‘metabolic inflexibility’) was observed in obese patients and is associated with intramyocellular lipid accumulation and insulin resistance (87). Various factors determine the metabolic flexibility of an organism, including nutrient availability, plasma FFA levels, the availability of adipose tissue for lipid storage and the status of physical activity (88). Another factor that may be implicated in metabolic flexibility is mitochondrial oxidative capacity. Although literature data are contradictory, it was proposed that muscle mitochondrial abnormalities influence metabolic flexibility to lipid and induce insulin resistance (88).

When calorie intake exceeds energy expenditure, as a consequence of a high-fat meal, or overfeeding, ample concentrations of energy substrates, such as glucose and FFAs, accumulate intracellularly in skeletal muscle. Increased entry of glucose results in augmented glycolytic flux and glucose oxidation, which overwhelms Krebs cycle and ETC capacity, ultimately leading to increased superoxide formation and oxidative stress (48). This excess ROS promotes the inhibition of the redox-sensitive glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GADPH) (89). The result of GADPH inhibition is the augmented flux of glucose metabolites through multiple metabolic pathways, including polyol pathway, AGEs formation, hexosamine biosynthesis pathway, increasing DAG synthesis via PKC activation leading to further exacerbation of oxidative stress and insulin-signaling interference (90).

Simultaneously, increased plasma FFA levels also disrupt skeletal muscle insulin signaling and promote
insulin resistance (91). Excess fat intake in conjunction with limited adipose tissue ability for fat uptake and storage leads to ectopic fat accumulation in skeletal muscle, mainly as long-chain fatty acyl-CoA, diacylglycerol (DAG), triacylglycerol (TAG) and ceramides (92). These lipid metabolites are active signaling molecules, which in turn impair signaling of insulin-stimulated intracellular pathways (93, 94, 95). Furthermore, FFAs directly activate inflammatory pathways, saturated fatty acids activate toll-like receptor (TLR-4) in skeletal muscle promoting c-Jun NH(2)-terminal kinase (JNK) and IκB kinase (IKK) complex activation, which results in degradation of the inhibitor of κB (IκB) and nuclear factor-κB (NFκB) activation, which in turn inhibit insulin receptor tyrosine phosphorylation (96). Finally, lipotoxicity is also associated with endoplasmic reticulum (ER) stress. During ER stress, misfolded proteins activate the ‘unfolded protein response’ (UPR), responsible for ER biogenesis, protein folding and degradation of aberrantly packaged proteins. If UPR is prolonged, the persistent oxidative protein folding machinery causes ROS production, with subsequent systemic release of FFAs and inflammatory mediators (97, 98).

Dietary habits can also affect physiological metabolic processes in skeletal muscle through direct alterations on mitochondrial biology and function (99). In normal healthy volunteers’ mitochondria isolated from skeletal muscle biopsies, fatty acid metabolite palmitoylcarnitine itself suppresses mitochondrial ATP production (100). In another study, volunteers fed an isoenergetic high-fat diet for 3 days showed downregulation of genes encoding for the mitochondrial biogenesis regulators PGC-1α and -1β and for genes encoding mitochondrial oxidative phosphorylation enzymes (101). Overall, overfeeding and increased dietary fat seems to promote mitochondrial dysfunction, with decreased ATP synthesis, impaired mitochondrial gene expression and increased ROS formation. As a result, a vicious cycle is initiated as these mitochondrial abnormalities further exacerbate the metabolic dysfunction of skeletal muscle (Fig. 5).

Liver

In a similar setting with skeletal muscle, overfeeding or dietary fat intake lead to increased FFA liver supply and intracellular lipid accumulation that have a detrimental effect in liver metabolism. Increased malonyl CoA levels in the liver promote de novo fatty acid synthesis and inhibit carnitine palmitoyltransferase-1 (CPT-1) activity. As a result, fatty acids cannot be oxidized in mitochondria and are diverted to other biosynthetic pathways, leading to formation of TAG, DAG and ceramides (102). In a rat model by Samuel et al., only 3-day high-fat feeding led to a three-fold increase of liver lipid accumulation without any significant increase in visceral or skeletal muscle fat content, suggesting that hepatic insulin resistance may precede systemic insulin resistance (103). As we mentioned above, these lipids initiate various inflammatory cascades that deregulate insulin signaling, including PKC and JNK pathways. In addition, in an experimental model by Soardo et al., FFA-exposed cultured hepatocytes displayed increased levels of oxidative and prothrombotic markers, such as NO, MDA and PAI-1 (104). Simultaneously, overfeeding and massive substrate supply to liver exposes ER to a heavy anabolic burden that consequently promotes protein misfolding and ER stress, which can promote ROS production and inflammatory signaling activation if persistently activated (102). Finally, intrahepatocellular lipid accumulation results in impaired insulin-mediated suppression of hepatic glucose production and dyslipidemia characterized by elevated hepatic VLDL triglyceride secretion combined with elevated HDL-cholesterol clearance (105).

Pancreatic β-cells

Oxidative stress can significantly compromise β-cell function, as pancreatic β-cells are innately more sensitive to oxidative stress. In an experiment by Maechier et al., β-cells exposed to hydrogen peroxide activated the production of p21 cyclin-dependent kinase inhibitor and decreased insulin mRNA, ATP and calcium flux reductions in mitochondria and cytosol (106). Furthermore, as shown by Tiedge et al., β-cells are lower in antioxidant enzyme levels (SOD, catalase and glutathione peroxidase) and more sensitive to ROS adverse actions (107). Therefore, oxidative stress, induced by elevated glucose and FFA levels, chronic inflammation and insulin resistance through the above mentioned mechanisms, acts directly in pancreatic cells and alters insulin secretion (6).

Chronic elevation of plasma glucose and FFA levels in diabetic patients has detrimental effects in pancreatic cell function (108). In cultured cells of islets or HIT cells, exposure to high concentrations of glucose and FFA levels led to a decrease in insulin gene activity and insulin mRNA and impairment of insulin signaling of
Nutrition and oxidative stress

Nutrition as a mediator of oxidative stress in metabolic disorders in women

Nutrition as a mediator of oxidative stress in female metabolic and reproductive disorders

Nutrition and calorie intake initiates a plethora of intracellular events in the major metabolic organs. Chronic hypernutrition, high-fat, high-carbohydrate meals, as well as dietary saturated fatty acids and glycoltoxins stimulate multiple intracellular pathways and propagate oxidative stress. The nutrition-induced oxidative stress is emerging as one of the principal parameters that give rise to multiple metabolic disorders in women, including obesity, insulin resistance, metabolic syndrome, and diabetes mellitus (Fig. 5).

In the pathogenesis of metabolic disorders and mediators of oxidative stress in women, the role of sex hormones and their imbalance has been clearly demonstrated by their impact on insulin signaling and glucose homeostasis (111). Estrogens and their metabolites have been linked to oxidative stress. Beyond their pure reproductive effects, they are important regulators of body’s metabolic function (112). Their receptors are present not only in reproductive tissues, but also in insulin-sensitive organs, including skeletal muscle, liver, and pancreatic β-cells, playing a modulatory role in insulin–glucose homeostasis (113). Analytically, in skeletal muscle, estradiol (E2) receptor α (ERα) has a positive effect in insulin signaling and GLUT4 expression (114). In skeletal muscle of ovariectomized mice, lipid metabolism was downregulated, inducing intracellular fat accumulation and activation of stress kinases (115). In addition, liver-specific ERα-knockout mice fed with a high-fat diet displayed decreased insulin sensitivity, as well as failure to suppress liver glucose production (116). Estrogen receptors are also present in pancreatic β-cells and enhance lipid homeostasis, insulin biosynthesis, and secretion and enhancing islet survival by protecting β-cell from oxidative stress and apoptosis (117).

Apart from the direct actions of estrogens on insulin-sensitive tissues, E2 can regulate metabolism and energy expenditure indirectly via mitochondrial function and oxidative stress (118). Specifically, E2 binding to nuclear and mitochondrial receptors promotes ATP production and mitochondrial biogenesis, alters mitochondrial ROS formation, activates PCG1a and induces an antioxidant response (119, 120, 121). Consequently, E2

the glucose-stimulated insulin secretion (109). Oxidative stress and aberrant free radical generation can be one of the underlying mechanisms of these derangements. In addition, hyperglycemia by itself can trigger increased intracellular mitochondrial ROS formation in pancreatic β-cells, promoting a local oxidative microenvironment, which in turn activates multiple metabolic pathways that further exacerbate oxidative stress (110), including chronic low-grade inflammation and AGE production, which further deteriorate β-cell function (108).
is highlighted as a natural, innate antioxidant agent of human body.

Regarding androgens, their metabolic role in females remains unclear. The majority of available data originate from women with polycystic ovary syndrome (PCOS), where hyperandrogenemia is present. In women with PCOS, it was shown that androgen excess per se can impair insulin action and promote insulin resistance (122, 123, 124). In addtition, in a mouse model by Liu et al., female mice with androgen excess experienced systemic oxidative stress and were subsequently predisposed to pancreatic β-cell failure and diabetes mellitus (125). However, in a more recent experimental model, female androgen receptor-knockout mice displayed increased body weight and body fat, decreased insulin sensitivity and marked dyslipidemia after 8-week high-fat diet, highlighting that not only androgen receptors may exert a protective effect in metabolic control but also how important is the role of balance between no androgens and excess of androgens (126).

During reproductive age, hormonal status and E2 abundance seem to favorably influence metabolism and oxidative balance. This is nicely depicted in experiments focusing on gender-dependent differences in nutrition-induced metabolic and oxidative derangements. First, in comparison to healthy young men, premenopausal women display significantly lower levels of oxidative stress (127). Analogous findings were reported postprandially, as women experienced lower oxidative stress than men, with regard to MDA and H2O2 levels, after ingestion of a lipid load in the form of heavy whipping cream (128). Furthermore, in an experimental model by Nickelson et al., high-fat diet was administered to weight-matched obese male and female mice. Females displayed greater adiposity and enlarged adipocyte size compared with weight-matched male mice. However, they remained more glucose tolerant, due to increased expression of adiponectin and reductions in immune cell infiltration and oxidative stress in adipose tissue (129). In a similar mouse model, males had a higher propensity to developing liver steatosis and insulin resistance after consumption of high-fat diet (130). Taken all the above into account, the metabolic and antioxidant properties of estrogens clearly protect premenopausal women from developing metabolic derangements and can be established as an important confounding factor in drawing definite conclusions about the role of nutrition-related oxidative stress in metabolic dysfunction.

Entering menopause, women experience a severe change in their reproductive potential, directly originating from estrogen–androgen imbalance with major defect of estrogen deficiency (131). Ovarian senescence affects many tissues and produces a variety of symptoms and signs. Loss of their main circulating estrogen, E2 leads to an abrupt reduction in metabolic rate, shift to increased central adiposity, dyslipidemia, progression of insulin resistance and metabolic syndrome, as well as adverse cardiovascular events (132).

In addition, the marked reduction in estrogen has been shown to increase levels of oxidative stress in the body, mainly through a decrease in antioxidant defenses (133). Women experience increased oxidative stress even during perimenopausal period, manifested by reduced PON1 A activity and elevated lipoperoxidation, DNA repair ability and total antioxidant status (134). Simultaneously, hormone replacement therapy is able to prevent and counteract such modifications by acting as regulators of key antioxidant gene expression (135, 136). Consequently, this pro-oxidant state that characterizes postmenopausal women potentiates the metabolic and endothelial dysfunction that characterizes postmenopausal women (132, 137).

The unique role of estrogen deficiency in metabolic and oxidative dysfunction during menopause was extensively evaluated in animal models, where artificial menopause and estrogen replacement were used to mimic hormonal background. The potent contribution of nutrition to this metabolic imbalance was also evaluated. In a study by Busserolles et al., ovariectomized female rats fed with high-sucrose diet displayed higher susceptibility to peroxidation, in comparison with intact females or ovariectomized females supplemented with estradiol (138). Furthermore, in another experimental model, ovariectomized rats fed with high-fat diet showed a marked reduction of whole blood antioxidants with a concomitant elevation of oxidant markers, as well as glucose intolerance and insulin resistance. Administration of soy isoflavones significantly improved these derangements (139). Analogously, Camporez et al. demonstrated that 4-week high-fat diet in ovariectomized mice led to increased body weight and fat mass, reduced whole-body energy expenditure, impaired glucose tolerance and whole-body insulin resistance in comparison to ovariectomized mice receiving hormone replacement therapy (140). Large clinical studies have also underlined the protective effect of estrogen against insulin resistance and metabolic dysfunction. In a population-based prospective cohort study, diabetes risk was reduced by 62% in women with current hormone replacement therapy (HRT) use compared with control
individuals (141). HRT also improved glucose control in women with preexisting diabetes and increased insulin sensitivity (142).

Concluding, calorie intake and its subsequent oxidative stress can significantly contribute to the development of various metabolic disorders in women. However, the hormonal background, with or without estrogens/with or without androgen excess, of every woman is a decisive denominator in this co-interaction, as hormonal fluctuations can uniquely determine her metabolic state.

**Nutrition as a mediator of oxidative stress in female reproductive disorders**

Oxidative metabolism is a critical intraovarian regulator of folliculogenesis. Free radicals and antioxidants seem to play a complex and multifunctional role in the ovarian environment during different stages of physiological oocyte maturation, as seen in Fig. 6. For example, on one hand, resumption of meiosis I of a primary follicle is induced by an increase in ROS and inhibited by antioxidants, suggesting that controlled ROS production by the pre-ovulatory follicle is an important promotor of the ovariolytic evolution, whereas on the other hand, ROS adversely affect meiosis II progression, leading to diminished gonadotropin and antisteroidogenic actions, DNA damage and inhibited protein ATP production (143). Apart from folliculogenesis, oxidative metabolism is also implicated in other functions of female reproductive system. In ovarian steroidogenesis, it has been shown that ovary overexposed to H$_2$O$_2$ led to impaired cholesterol utilization and protein synthesis, mainly through altered production of steroidogenic acute regulatory protein (StAR) (143). In addition, exposure to oxidative stress before fertilization leads to disrupted meiotic spindle and increased risk for abnormal zygote formation, especially when antioxidant defenses are insufficient (144). Finally, NO seem to carry a critical, regulatory role during embryonic development and implantation (145). Although its function is not established, NO seems to contribute as an anti-platelet agent, as well as a regulator of cyclic GMP, which mediates estrogen-stimulated uterine secretory response at the implantation site (146). Overall, oxidative equilibrium in the ovarian microenvironment and preservation of a delicate oxidative balance are crucial in order to secure normal ovum function and development.

Consequently, a plethora of studies have been conducted so far in order to explore the putative role of oxidative stress in fertility. The majority of them involve women undergoing assisted reproductive techniques (ART), where various systemic and follicular fluid markers of oxidative stress were correlated with fertilization and pregnancy outcomes. Specifically, increased levels of MDA, ROS, NO and lipid peroxidation (LPO) in follicular fluid of women undergoing ART were associated with lower ovarian response, poorer embryo quality, decreased fertilization and pregnancy rates (147, 148, 149). On the other hand, follicular fluid total antioxidant capacity (TAC) of patients undergoing IVF was positively associated with success rates (150, 151), whereas enhanced blood plasma antioxidant status was shown to be beneficial in achieving pregnancy in these women (152).

The role of nutrition and its impact on inducing local oxidative stress in the ovarian milieu has also been investigated, but to a much lesser extent. In an experimental model by Valckx et al., early secondary murine follicles were cultured in vitro in the presence of FFAs until the antral stage and it was shown that elevated FFA concentrations can potentially impair fertility, by altering follicular physiology and reducing oocyte developmental competence (153). Analogously, an observational study of 236 women undergoing assisted reproduction program revealed that fatty diet can induce oxidative stress in oocyte environment and negatively influence embryonic development (154). However, Kazemi et al. failed to prove a potential relationship between total calorie intake, BMI and physical inactivity with oxidative biomarkers in follicular fluid (155).

Finally, increased dietary AGE consumption contributes to increased AGE deposition in ovarian tissue, promoting significant perturbations in ovarian microenvironment and ovulatory dysfunction (156). Recently, different research groups have investigated the potential role of AGE-RAGE system in female infertility (157). Jinno et al., in a retrospective analysis of women undergoing IVF, have documented that serum and follicular fluid AGE levels negatively correlated with follicular growth, fertilization rates and embryonic development. What’s more, lower follicular fluid AGE levels were the most significant predictors of pregnancy outcomes (158). In another study of women undergoing IVF, follicular fluid levels of soluble form of RAGE (sRAGE) significantly correlated with conception rates (159). Finally, sRAGE seems to be positively correlated with AMH, a well-known marker of ovarian reserve (160). Overall, intraovarian AGE accumulation can be a decisive parameter in the initiation of ovarian dysfunction, which can potentially lead to infertility.

Concluding, oxidative metabolism has a unique role in female reproductive physiology (Fig. 6). There is a delicate, marginal threshold distinguishing beneficial and
Nutritional oxidative stress: an important intraovarian regulator in female reproductive disorders

Detrimental effects of pro-oxidants
- Folliculogenesis: ROS affect adversely meiosis II
- Ovarian steroidogenesis: impaired cholesterol utilization and protein synthesis
- Fertilization: oxidative stress leads to disrupted meiotic spindle and increased risk for abnormal zygote formation

Favorable effects of pro-oxidants
- Folliculogenesis: ROS induce resumption of meiosis I
- Controlled ROS induce theca interstitial cell proliferation
- Fertilization/implantation: NO stimulates estrogen-stimulated uterine secretory response

Ovarian ageing, Infertility, PCOS, Endometriosis

Figure 6
Nutritional oxidative stress: an important intraovarian regulator in female reproductive disorders. Dysequilibrium between pro-oxidants affects intraovarian environment and alters female reproduction. Nutritional oxidative stress can augment detrimental effects of pro-oxidants and mediate the manifestation of various reproductive disorders. (ROS: Reactive oxygen species, NO: nitric oxide, PCOS: polycystic ovary syndrome).

harmful effects of oxidative stress and tightly controlled pro-oxidant:antioxidant ratio is mandatory to secure normal ovarian function. Therefore, oxidative stress could be a potent, underlying mechanism of various reproductive abnormalities (5). However, data establishing solid conclusions about the role of nutrition-promoted oxidative stress in female reproductive dysfunction, as a therapeutic target, are limited.

Ovarian aging
Ovarian functional decline with aging has been so far extensively characterized in terms of gradual depletion of ovarian follicles and reduced ability to produce oocytes competent for fertilization and further development (161). Oxidative stress-induced ovarian aging originates from a continuous imbalance, derived by excessive ROS generation combined with antioxidant levels decline (162).

Analytically, serum concentrations of inflammatory cytokines and pro-oxidant biomarkers such as oxidized lipoproteins (ox-LDL), 4-hydroxynenal and MDA were found to be higher in postmenopausal women than in premenopausal women (163). In contrast, GSH and glutathione transferase, which are effective in the removal of free radicals, are reduced in oocytes with age (164). With the weakening of the antioxidant defense, aging also occurs in granulosa cells, accompanied by Cu/Zn superoxide dismutase, Mn superoxide dismutase and catalase downregulation (165). Similarly, as shown by a mouse model by Lim et al., significant age-related increases in oxidatively damaged lipids, proteins and DNA are observed in different ovarian compartments, including granulosa cells and ovarian interstitial tissue, along with alterations of antioxidant enzyme expression (166). Finally, hormonal alterations that accompany ovarian aging, such as the marked reduction in estrogen, have been shown to increase levels of oxidative stress in the body (167).

Furthermore, AGEs may also be involved in the process of ovarian aging. A study by our group demonstrated that AGEs are present in normal ovarian tissue obtained from reproductive-aged women, whereas RAGE was highly expressed in the ovary being present in granulosa theca interna, endothelial and stromal cells (168). In addition, increased levels of pentosidine were observed in the primordial, primary and atretic follicles of premenopausal women, findings that suggest a possible correlation of AGEs with ovarian aging (169). Consequently, potential accumulation of these compounds in the ovary across life span may initiate adverse molecular intraovarian events, such as compromised efficiency of vascularization and activation of oxidative stress response through RAGE interaction, and ultimately trigger ovarian dysfunction (170). Finally, the activity and expression of glyoxalase-1 (GLO1), a powerful enzymatic system of AGE scavenging, was also found to be decreased in aged ovaries of mice (171).

Overall, experimental data regarding the role of oxidative stress in ovarian aging are only indicatory and further investigation of the network involving mitochondrial dysfunction and ROS overload in the follicle should be encouraged. The role of nutrition and the direct effects of nutrition-induced oxidative stress in the ovary have not been adequately evaluated and
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various pro-oxidant biomarkers have been shown to be altered in PCOS. Specifically, in a recent meta-analysis by Murri et al., homocysteine, malondialdehyde (MDA) and asymmetric dimethylarginine (ADMA) levels were shown to be elevated in women with PCOS (180). Conversely, levels of antioxidants also seem to be affected in women suffering from PCOS, conserving the redox imbalance and perpetuating oxidative stress. Total antioxidant capacity (TAC), an aggregative index of plasma antioxidant state, which represents the ability of human body to eliminate free radicals, was found to be decreased in women with PCOS (181, 182), whereas various abnormalities were also detected in the concentrations of enzymatic antioxidants, such as paraoxonase-1 (PON-1) and glutathione, whose activities were shown to be decreased, and superoxide dismutase (SOD), whose activity was enhanced in women with PCOS (180, 183, 184).

Nutrition-induced oxidative stress, through postprandial hyperglycemia, has also been studied in PCOS. Specifically, increased ROS production by monocytes in response to hyperglycemia was observed in women suffering from PCOS, independent of the presence of obesity and abdominal adiposity, via stimulating secretion of inflammatory markers (i.e., TNF-α and NF-κB) and activation of NADPH oxidase (185, 186). What’s more, hyperglycemia was also shown to alter the action of enzymatic antioxidants, such as glutathione peroxidase (GPx) (187), and hyperandrogenemia, which predominates in PCOS, seems to significantly contribute to increased sensitization of leukocytes to hyperglycemia and the concomitant upregulation of the expression of various inflammatory markers even in lean women with PCOS (188, 189). Interestingly, apart from insulin sensitivity, it was recently shown by Malin et al. that hyperglycemia-induced inflammation has an adverse impact on pancreatic β-cell function, further exacerbating glycemic dysregulation in women with PCOS (190, 191).

PCOS could serve as a model in which reproductive and metabolic abnormalities could be uniquely linked to oxidative stress, as oxidative stress contributes to both reproductive and metabolic dysfunctions that characterize women suffering from PCOS. Regarding metabolic signaling, PCOS is commonly accompanied by obesity, abdominal adiposity, insulin resistance and endothelial dysfunction (176). As discussed above, oxidative stress is a common denominator of all these pathophysiological processes and seems to drive analogous detrimental cellular events in women with PCOS, as well (48). Regarding reproduction, accumulating data highlight the role of oxidative stress.

Unexplained infertility

Idiopathic (unexplained) infertility is diagnosed by exclusion and is defined as the inability to conceive after 12 months of timed, unprotected intercourse where tests have been performed on both partners to rule out known causes of infertility, including but not limited to anovulation and sperm defects (5). Although its etiology remains unclear, it is believed that oxidative stress significantly contributes to its pathogenesis.

Total antioxidant status was found to be lower in peritoneal fluid of women with idiopathic infertility compared with fertile controls (172), whereas elevated levels of ROS in the peritoneal fluid of women with idiopathic infertility were also reported by Wang et al. and Polak et al. (172, 173). However, a study in which N-acetyl cysteine (NAC), a potent antioxidant compound, was administrated with clomiphene citrate for ovulation induction in women with unexplained infertility failed to improve ovulation rates in comparison to women treated only with clomiphene citrate (174).

Human studies regarding the role of nutrition-induced oxidative stress in infertility are limited. The majority of them have focused on follicular fluid composition in women undergoing IVF where follicle maturation is stimulated with exogenous hormones, creating a milieu that differs from the FF of women without ovarian stimulation. Therefore, future, prospective, well-designed pregnancy studies, in which dietary interventions and biological sample examinations can take place, are mandatory in order to investigate deeper the field of diet-induced oxidative stress in female infertility.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies of premenopausal women, encountered in everyday clinical practice (175). Its etiopathophysiological core remains vague; however, gonadotropin-secretory alterations, androgen excess, insulin resistance and low-grade inflammation, in conjunction with the pivotal contribution of genetic and environmental parameters, are all involved in the interplay net of the syndrome (176, 177). Recently, oxidative stress has also been highlighted as another potent modulator of PCOS (178, 179).
in the microenvironment of the ovary in PCOS. Women with PCOS displayed increased follicular fluid levels of ROS and MDA, as well as decreased total antioxidant capacity (TAC), which were directly associated with lower rates of oocyte maturation and fertilization, poor embryo quality and decreased pregnancy rates (146, 192, 193). In fact, in a study by Karuputhula et al, various markers of oxidative stress were assessed in different populations of infertile women who underwent IVF (194). Among the whole cohort, women with PCOS displayed the highest levels of ROS in granulosa cells and were accompanied by poorer fertilization rates (194). Finally, we should mention a recent study of a hyperandrogenism-induced murine model of polycystic ovary by Rezvanfar et al., in which various markers of oxidative stress were found to be altered both in serum and follicular fluid, derangements that also prevail in ovarian aging process. Not surprisingly, it is implied that PCOS may induce acceleration of aging process and early washup of ovarian reserve (195). However, clinical data from human studies do not seem to confirm an early menopause in women with PCOS (196, 197).

Equally significant are the data on AGEs, derived from studies in PCOS women. AGEs are known to be extremely inflammatory with dominant pro-oxidant capacity, produced endogenously as well as deriving mostly from diet. AGEs were shown to be distinctively elevated in women with PCOS, independent of the presence of obesity and insulin resistance, exerting unfavorable effects in both reproductive and metabolic function of these women (198). Also, AMH correlates strongly with AGE levels in PCOS women, a finding in human studies indicating the potential role of oxidative stress in the follicular maturation process (199).

AGEs have a direct impact on the ovarian cells of women with PCOS. Specifically, female high-AGE-fed rats displayed increased deposition of AGEs and RAGE in theca and granulosa cells, as well as downregulated ovarian glyoxalase-1 activity, a protective enzyme against glycation (200, 201). PCO ovaries displayed increased AGE deposition in theca, granulosa and endothelial ovarian cells and higher expression of RAGE as well as NF-κB p65 subunit in granulosa cells (168). Accumulating AGEs interfere with intracellular ovarian signaling pathways, specifically with insulin signaling in granulosa cells with potential interference in ovarian dysfunction in PCOS (202). Concerning metabolic dysfunction, it is well established that AGEs are closely linked to insulin resistance. In a mouse model by Cai et al., it was demonstrated that mice fed with a high-AGE diet demonstrated insulin resistance, abdominal adiposity and eventually diabetes, in comparison with mice fed with an isocaloric AGE-free diet (203). In an analogous human model by Tantalaki et al., lower dietary AGE intake in women with PCOS resulted in a parallel decrease in serum AGE, insulin levels, HOMA-IR and oxidative stress markers, depicting a significant improvement of their metabolic profile (204).

Oxidative stress holds a respectable share in the etiology of metabolic and reproductive aberrations in PCOS, as these women display hyperandrogenemia and insulin resistance, both of which are aggravators of the oxidative status and vice versa. Although more research is mandatory in order to set solid knowledge, it becomes evident that oxidative stress, in conjunction with the rest etiological parameters, orchestrates the pathogenetic process in reproductive as well as in metabolic abnormalities in women with PCOS.

### Endometriosis

Endometriosis is a benign gynecologic disorder of unknown etiology, in which endometrial tissue is present outside the uterus, most often in ovaries, abdominal viscera, urinary tract or even in lungs. Endometriosis affects 6–10% of women of reproductive age and has been associated with infertility. Various theories have been postulated regarding the pathophysiology of endometriosis, one of which is oxidative stress (5).

After bleeding and hemolysis in endometriosis, the pro-oxidant hemoglobin transfers heme and iron derivatives to endometriotic lesions or peritoneal cavity. As free heme and iron are considered generally toxic compounds, autoxidation of hemoglobin takes place, leading to excessive production of ROS that in turn activates multiple signaling pathways, cytokine release and apoptosis. Cellular oxidant property and antioxidant defenses are decisive in determining the extent of cell death (205).

A plethora of scientific studies have focused on investigating the role of nutrition-related oxidative stress in endometriosis. Data are mainly contradictory in bibliography. Although some studies failed to observe increased oxidative stress in the peritoneal fluid or circulation of patients with endometriosis, others have reported increased levels of oxidative stress markers in those with the disease (5). In a recent study by Singh et al., increased concentration of ROS, NO, LPO, iron, lead, cadmium and reduced levels of TAC, SOD, catalase, GPx, glutathione reductase (GR), vitamins A, C, E, copper, zinc...
and selenium was observed in women with endometriosis undergoing IVF (149). Analogously, the peritoneal fluid of these patients has also been found to contain high concentrations of MDA, proinflammatory cytokines (IL-6, TNF-alpha and IL-beta), angiogenic factors (IL-8 and VEGF), MCP-1 and ox-LDL (206). Furthermore, endogenous antioxidant compounds are also disrupted in women suffering from endometriosis. Specifically, lower plasma SOD concentration, lower follicular fluid vitamin C levels and imbalanced intrafollicular thiol-redox system were detected in infertile women with endometriosis, in comparison with controls (207, 208). In a study by Mier-Cabrera et al., when a high-antioxidant diet was administered in women with endometriosis, peripheral oxidative stress markers, including MDA and lipid hydroperoxides, were significantly attenuated and antioxidant markers, specifically SOD and GPx, were enhanced (209). However, laboratory data were not correlated with clinical outcomes, in order to reach possible links and conclusions.

Long-term effects of nutrition in oxidative homeostasis

Nutrition-induced oxidative and inflammatory milieu in an acute setting can modify intracellular and extracellular physiological functions. When these derangements are repeated, they support a sustained oxidative and inflammatory status, which, in turn, can predispose to a variety of diseases.

In a study by Vlassara et al., in which high-AGE diet fed for 6 weeks in diabetic patients resulted in a significant increase in serum TNF-a, CRP and VCAM-1 levels depicted the potent inflammatory actions of AGEs that can potentially lead to tissue injury (19). Simultaneously, in female high-AGE-fed mice, increased deposition of AGEs and RAGE in ovarian tissues was observed, altering the cellular milieu and downregulating glyoxalase-1, a protective enzyme against glycation, ultimately leading to ovarian dysfunction (200, 201).

On the other hand, restricted calorie nutritional patterns can exert the exactly opposite effect, securing oxidative balance and promoting cell longevity. For example, 6-month caloric restriction attenuated oxidative stress and decreased significantly fasting insulin levels and body core temperature (two markers of longevity) in healthy individuals (210). In addition, in a study by Ceriello et al., diabetic patients following a Mediterranean diet for 3 months, enriched in monounsaturated fatty acids or polyunsaturated fatty acids and polyphenols, displayed increased plasma antioxidant capacity and improved basal endothelial function, in comparison with controls (211).

Overall, it becomes clearly evident that nutrition acts catalytically in the maintenance of oxidative balance both in an acute and in a chronic setting. Nutritional divergences can easily violate this cellular balance, initiate detrimental pathophysiological pathways and promote the occurrence of various diseases in women.

Conclusion

Nutrition constitutes one of the major modulators of oxidative stress in human body. Nutrient intake and its accompanying postprandial oxidative stress initiate a clustering of molecular changes in the main signaling pathways of various organs, unfavorably alter the cellular milieu. Specifically in women, nutritional oxidative stress modulates and interferes directly and indirectly with the metabolic and reproductive functions, which are ultimately compromised. Nevertheless, the exact pathophysiological links are still escaping, making targeted therapeutic modalities a challenging field. Therefore, in women with metabolic and reproductive disorders, modification of nutritional habits by reduction of food quantity remains the most well-studied factor, but the quality and the timing of meals should also be taken into account as are currently considered as contributors.

Declaration of interest

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