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REVIEW

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# The effect of diet on oxidative stress and metabolic diseases—Clinically controlled trials

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## Abstract

Oxidative stress is associated with several chronic diseases. It is acknowledged that molecules damaged by reactive oxygen species activate the inflammatory process and that this response increases the production of free radicals. Modifications in a diet can improve or decrease redox state markers. The aim of this revision was to provide an update of clinical controlled trials, to assess changes in diet and markers of oxidative stress in subjects with metabolic diseases. They were investigated randomized controlled intervention studies (RCTs) published in MEDLINE (U.S. National Library of Medicine, National Institutes of Health) that were conducted in subjects with obesity, hypertension, diabetes, or dyslipidemia; with dietary intervention; where markers of oxidative stress have been evaluated and published in the last 5 years. Food antioxidants, hypocaloric diets with loss of adipose tissue, substitution of animal protein by vegetable, and changes in the microbiota improve antioxidant status in people with chronic disease.

## Practical applications

Hyperglycemia in diabetes mellitus and adipose tissue in obesity are known to trigger oxidative stress. Oxidative stress, in turn, decreases insulin sensitivity and favors an inflammatory state producing adhesion molecules. Oxidative stress and adhesion molecules, can increase blood pressure and oxidation of lipoproteins, that ultimately could lead to a cerebrovascular event. Consumption of high-antioxidant and polyphenol foods increases plasma antioxidant capacity and decreases oxidative stress markers in people with diabetes, obesity, hypertension, and hypertriglyceridemia. In addition, weight loss caused by caloric restriction with or without exercise increases the endogenous antioxidant capacity. Therefore, it is likely that the combination of a hypocaloric diet with a high content of antioxidants and polyphenols will have a greater effect. Other dietary changes with antioxidant effect, such as the substitution of animal for vegetable protein or the addition of fiber, might be mediated by changes in the microbiota. However, this aspect requires further study.

KEYWORDS

dyslipidemia, food, hypertension, nutrition, obesity, overweight

  

## 1 | INTRODUCTION

The origins of oxidative stress have been related to nutrition. The excessive consumption of food generates an energy intake above the energy expenditure, that implies at the metabolic level the reduction of oxygen to the superoxide ion, which is a free radical (Ceriello & Motz, 2004).

To protect the organism from the harmful effects of reactive species, there is an antioxidant defense system, which is composed of enzymes (Lushchak, 2014; Srivastrava & Kumar, 2015). Considering the variety of enzymes and the balance between pro-oxidant and antioxidant compounds, it has been described scales of intensity ranging from physiological oxidative stress (eustress) to excessive and toxic oxidative stress (distress) (Lushchak, 2014). The molecular-level damage that can occur corresponds to the modification (structural and functional) over macromolecules, such as DNA, proteins, and lipids (Sies, Berndt, & Jones, 2017).

The molecules involved in oxidative stress include reactive oxygen species (ROS), reactive nitrogen species (RNS), reactive sulfur species (RSS), reactive carbonyl species (RCS), and reactive selenium species (RSeS), which may include free radicals or nonradicals (Sies et al., 2017). Inflammatory processes have been related to oxidative stress by increasing ROS production (Alfadda & Sallam, 2012). Due to the above, an additive effect relationship has been created where oxidative stress and the inflammatory process behave symbiotically (Lugrin, Rosenblatt-Velin, Parapanov, & Liaudet, 2014).

Some research has related oxidative stress with metabolic diseases, among which are excess weight (obesity/overweight), diabetes, hypertension, and dyslipidaemia (Devaraj, Leonard, Traber, & Jialal, 2008). It has now been shown that chronic exposure to high concentrations of glucose, triglycerides, and free fatty acids increases oxidative stress through the activation of NADPH oxidase (Furukawa et al., 2004); on the other hand, various foods have antioxidant compounds.

Since the diet is related to metabolic diseases, as well as oxidative stress, it is relevant to take preventive actions which can be achieved through food (Srivastrava & Kumar, 2015). Therefore, the aim of this work was to conduct a review of controlled, randomized clinical trials evaluating changes in diet and markers of oxidative stress in subjects with metabolic diseases, published in MEDLINE (U.S. National Library of Medicine, National Institutes of Health) in the last 5 years and that have been performed in subjects with obesity, hypertension, diabetes, or dyslipidemia; with dietary intervention (food supplements, powders, and common food or drinks).

## 2 | OXIDATIVE STRESS

Sies in 1985 coined the term of "Oxidative Stress" to describe the imbalance between the oxidant molecules and the antioxidant mechanisms in favor of the first one, which leads to a disruption of the signal and redox control and/or molecular damage (Sies, 2015).

Molecular damage corresponds to the structural and functional modification that excess free radicals cause to macromolecules such as DNA, proteins, and lipids in a cell (Sies et al., 2017). The distinction between oxidative stress, which is a reversible situation, and oxidative damage as an irreversible situation should be considered (Srivastrava & Kumar, 2015).

The molecules involved in redox state, and therefore in oxidative stress, include ROS, RNS, RSS, RCS, and RSeS, which may include free or nonradical radicals (Sies et al., 2017).

Free radicals are molecules that contain an unpaired electron in an atomic orbit. This characteristic provides common properties of most free radicals, which are unstable and very reactive, since they can donate or accept an electron from other molecules (Lobo, Patil, Phatak, & Chandra, 2010).

The main ROS are free radical's superoxide anion ($O_2^{-}\cdot$), hydroxyl radical (OH·), peroxyl radical (ROO·), and alkoxyl radical (RO·). Other molecules derived from oxygen that are not free radicals, but are very reactive and unstable, are hydrogen peroxide ($H_2O_2$), organic hydroperoxide (ROOH), singlet oxygen ($^1O_2$), and hypochlorous acid (HClO). Nitric oxide (NO·), nitrogen dioxide ($NO_2\cdot$), nitrite ($NO_2^{-}$), nitroxyl anion ($NO^{-}$), peroxynitrite ($ONOO^{-}$), peroxynitrate ($O_2NOO^{-}$), and nitrosoperoxycarbonate ($ONOOCO_2^{-}$) are RNS (Lobo et al., 2010; Sies et al., 2017).

The formation of free radicals derives from essential metabolic processes in the human body and can also come from external sources such as exposure to x-rays, ozone, smoking, pollutants, and chemical products, among others. The physiological sources of free radicals are: the mitochondria; the auto-oxidation of flavins, thiols, and small molecules such as catecholamines; the metabolism of arachidonic acid; endoplasmic reticulum and the nuclear membrane transport system; peroxisomes, respiratory burst of polymorphonuclear cells (PMN), and macrophages; transition metals such as iron and copper; the enzymatic reactions of hypoxanthine and xanthine oxidase; and cytochrome P-450 system (Lobo et al., 2010; Valko et al., 2007).

To protect the organism from the harmful effects of reactive species, there is an antioxidant defense system, which is composed of enzymes: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST); endogenous compounds such as uric acid, glutathione, melatonin, chelating proteins (transferrin, lactoferrin, and ceruloplasmin). Thus, exogenous molecules such as β-carotene, ascorbate, α-tocopherol, anthocyanins, and polyphenols (Lushchak, 2014; Srivastrava & Kumar, 2015).

Living organisms have finely regulated systems to maintain very low levels of reactive species. However, in certain circumstances, this balance may be disturbed by: (a) an increase in the level of endogenous and exogenous compounds that enter autoxidation together with the production of reactive species; (b) depletion of reserves of endogenous and exogenous antioxidants; (c) inactivation of antioxidant enzymes; and (d) decreased the production of enzymes and antioxidant molecules (Lushchak, 2014).

Cell membranes are particularly susceptible to oxidative damage, because they contain polyunsaturated fatty acids in the

phospholipid bilayer. The general process of lipid peroxidation consists of three stages: initiation, propagation, and termination (Catalá, 2010).

The initiation phase of lipid peroxidation involves that the methylene between the double bonds losing a hydrogen, which produces a radical in the carbon. Thus, a peroxide radical is originated, which can take a hydrogen from another lipid, which propagates the lipoperoxidation reaction. During the peroxidation of lipids, aldehydes are generated by fatty acid fragmentation. This fragmentation has as consequences that the phospholipid now has a shortened chain that affects the organization of the lipid bilayer and causes a greater permeability of the membrane, as well as the release of aldehydes that are highly reactive molecules. Among the aldehydes produced are 4-hydroxy-2-nonenal (HNE), 4-hydroxy-2-hexenal (HHE), acrolein, and malondialdehyde (MDA); HNE is the main product of n-6 fatty acid peroxidation, while HHE is the main product of n-3 fatty acids (Catalá, 2010). These can spread through cell membranes, which is why they are found extracellularly (Madian & Regnier, 2010).

Proteins are biomolecules susceptible to the effects of oxidative stress, both primary and secondary. The first is about the direct action of OH• on any amino acid, taking preference for amino acids with electron-rich side chains (tryptophan, tyrosine, histidine, methionine, cysteine, and phenylalanine). Secondarily, aldehydes such as MDA, acrolein, HHE, and HNE oxidize cysteine, histidine, or lysine (Witz, 1989). The products obtained from the primary and secondary reactions generate products called carbonylated proteins (PCO). It is considered that the effect of protein carbonylation on function greatly affects two main properties: the catalytic activity of proteins and/or protein–protein interactions (Hauck & Bernlohr, 1986). Although the modification can be low (5%), when multiple proteins of a metabolic pathway are simultaneously carbonylated, the pathway can be considerably affected.

Damage to DNA results in mutations and cell death. Although oxidative damage can occur in both purines and pyrimidines, guanine has the lowest ionization potential, which is why is more susceptible to oxidative damage (Sies et al., 2017). Oxidation between C4 and C8 produces the compound 8-oxo-7,8-dihydroguanidine (also called 8-hydroxyguanine or 8-oxoguanine), which combines with adenine instead of with cytosine and therefore generates transient mutations after replication (Freudentahal et al., 2015). The accumulation of 8-oxoguanine causes mitochondrial dysfunction and is oncogenicity (Leon et al., 2016).

Since the redox state is a dynamic process, oxidative stress can be measured through the capacity or overall antioxidant status, the measurement of the activity of antioxidant enzymes, reactive species or damaged molecules. The main markers used are presented in Table 1.

**TABLE 1** Oxidative stress markers

| Capacity antioxidants | Antioxidant enzymatic | Reactive species | Markers of oxidative damage | | |
|---|---|---|---|---|---|
| | | | Lipids | DNA/RNA | Proteins |
| Total Antioxidant capacity (TAC) | Superoxide dismutase (SOD) | Metabolites derived from reactive oxygen species (d-ROM) | Malondialdehyde (MDA)/Substances reactive to thiobarbituric acid (TBARS) | 8-oxo−7,8-dihydroguanidine, 8-hydroxyguanine or 8-oxoguanine (8-OH-dG) | Carbonylated proteins (PCO) |
| Total oxidative stress (TOS) | Catalase (CAT) | Peroxide ($H_2O_2$) | Oxidized LDL (ox-LDL) | Comet assay | Fluorescent oxidation products (FOP) |
| Iron-reducing antioxidant potential (FRAP) | Glutathione peroxidase (GPx) | | Lipid hydroperoxides (LHP) | Fluorescent oxidation products (FOP) | |
| Absorption capacity of oxygen radicals (ORAC) | Glutathione S-transferase (GST) | | 4-hydroxy−2-nonenal (HNE) | | |
| Total antioxidant status (TAS, TAOS) | Glutathione reductase (GR) | | 4-hydroxy−2-hexenal (HHE)(ORG) | | |
| | Oxidated glutathione (GSSG)/ Reduced Glutation (GSH) | | F2α-isoprostanes (*eg* 8-epi $PGF_{2\alpha}$) | | |
| | Thioredoxin reductase 1 (TXNRD1) | | Acrolein | | |
| | Thioredoxin (TRX) | | Fluorescent oxidation products (FOP) | | |

*Note:* Catalá (2010), Vetrani et al. (2012), Sies et al. (2017).

## 2.1 | Inflammation and oxidative stress

Inflammation is an adaptive response that occurs after the loss of the integrity of tissues and which has the purpose of restoring

homeostasis (Goldszmid & Trinchieri, 2012). Inflammation starts with a danger signal, the signal transmission, the production of mediators, and the activation of cellular effectors (Medzhitov, 2008), all of which can be affected, in various degrees, by reactive species.

The endogenous molecules that can activate the inflammatory response are called molecular patterns associated with damage (DAMPS), which includes extracellular, intracellular, and mitochondrial proteins (Lugrin et al., 2014). However, also oxidized molecules such as phospholipids, low-density lipoproteins, cholesterol esters, and DNA can activate the inflammatory response (Lugrin et al., 2014). Moreover, some nutrients such as high glucose content and long-chain fatty acids (Tack, Stienstra, Joosten, & Netea, 2012) are also recognized by receptors that trigger an inflammatory response.

Inflammation increases the production of ROS (Alfadda & Sallam, 2012) and oxidative stress can cause changes in lipids and proteins that act as DAMP and even promote apoptosis and necrosis (Brow, 2007).

Oxidative stress can modulate numerous transcription factors sensitive to the redox state, including the nuclear factor NFκB, activating protein 1 (AP-1), and the early growth response 1 (EGR1), which act collectively to trigger the inflammatory process (Lyer, Fairlie, Prins, Hammock, & Brown, 2010).

Both processes, oxidative stress and inflammation, contribute to each other, thus establishing a vicious cycle capable of perpetuating the inflammatory response (Lugrin et al., 2014).

## 3 | METABOLIC DISEASES

Noncommunicable diseases (NCDs), also known as chronic diseases, tend to be long-lasting and result from the combination of genetic, physiological, environmental, and behavioral factors. The main NCDs are cardiovascular diseases, diabetes, obesity, dyslipidaemia, and cancer. According to the World Health Organization (WHO), these diseases mainly affect low- and middle-income countries in worldwide, where there are more than 75% deaths from NCDs (32 million).

Inadequate or unhealthy diets, physical inactivity, high blood pressure, increased glucose, and lipids in the blood and obesity are the metabolic risk factors, affecting all age groups in different regions and countries.

Worldwide, 19% of deaths are attributed mainly to the increase in blood pressure, the main metabolic risk factor followed by overweight and obesity, and finally to the increase in blood glucose (OMS, 2018).

Since 1975, obesity has tripled worldwide making it in 2016, 1,900 million overweight adults over the age of 18, from which 650 million present obesity; thus, creating a prevalence of 39% overweight and 13% obese (OMS, 2018). According to the Organization for Economic Cooperation and Development (OECD), Mexico occupies the second place in the world with 32.4% and if this continues, it is believed that Mexico will increase up to 39% of obesity by 2030 (OCDE, 2017).

Another metabolic risk factor, such as diabetes, has increased from (4.7%) 108 million in 1980 to 463 million in 2019. It is known that diabetes is an important cause of blindness, kidney failure, myocardial infarction, strokes, and amputations of the lower limbs, among others. By 2019, diabetes was the cause of deaths of 4.2 million people and it is believed that, in 2030, it will be the seventh cause of mortality worldwide (IFD, 2019).

According to the World Health Organization (WHO), more than one in five adults suffers from high blood pressure, a disorder that causes approximately half of all deaths from stroke or heart disease. The complications derived from hypertension are the cause of 9.4 million deaths every year around the world. High blood pressure (HBP) is a very common condition and the main factor related to mortality worldwide, this being more than 19 million people worldwide. Another metabolic disease are the dyslipidaemias, which are considered a modifiable risk factor of coronary disease, and many times depend on age. However, the younger the person, the greater the negative impact on life expectancy (Gómez-Avellaneda & Tarqui-Mamani, 2017). There are some studies that report the prevalence of hypertriglyceridemia in different countries, among which are India with 29.5% (Joshi et al., 2014), the United States with 25.1% in 2015 (Carrol, Kit, & Lache, 2015), and 24% Brazil (De Carvalho-Vidigal, Bressan, Babio, & Salas, 2013). Among the Mexican population, it is known that there are more than 14 million people with dyslipidaemias between the 20 and 69 years of age (Barba, 2018; García-García et al., 2008).

## 4 | RELATIONSHIP BETWEEN OXIDATIVE STRESS, INFLAMMATION, AND METABOLIC DISEASES

The excessive consumption of food, where the energy intake exceeds the energy expenditure, leads to an overload of free fatty acids and glucose in the mitochondria that are converted to acetyl coenzyme A(CoA). During the oxidation of acetyl CoA in the Krebs cycle reduced NADH + $H^+$ coenzymes are produced, which are dissipated in the electron transport chain to produce ATP. However, when they are in excess, membrane potential increases to the point that complex III stagnates, resulting in increased half-life of coenzyme Q. Increased availability of coenzyme Q leads to greater reduction of oxygen to superoxide ($O_2^{-}\cdot$) (Ceriello & Motz, 2004).

As a compensatory mechanism, the oxidation of fatty acids in the mitochondria is inhibited, accumulating in the cytoplasm that inhibits the translocation of the GLUT4 insulin-dependent glucose transporter, which would cause insulin resistance in adipose and muscle tissues (Ceriello & Motz, 2004). On the other hand, noninsulin-dependent cells such as ß and endothelial cells could not regulate the flow of nutrients to the mitochondria, which would increase the production of free radicals and oxidative damage (Ceriello & Motz, 2004).

### 4.1 | Obesity, oxidative stress, and inflammation

The excessive consumption of nutrients has an increase of adhesion molecules, which leads to the filtration of adipose tissue with macrophages. The accumulation of macrophages and adipocytes releases numerous proinflammatory cytokines including TNF-α, IL-6, leptin, resistance, visfatin, adiponectin, monocytic chemotactic protein-1 (MCP-1), and inhibitor of plasminogen activator-1 (PAI-1), which serve to recruit additional immune cells and promote the filtration of macrophages, which perpetuates the state of inflammation (Goossens, 2008; Lyer et al., 2010). The circulating levels of IL-6 and TNF-α are strongly correlated with the increase in adipose mass (Bastard et al., 2000). It has been shown that body fat and waist circumference is positively associated with endothelial dysfunction derived from oxidative stress, catalase activity, and thiobarbituric acid reactive substances (TBARS) (Furukawa et al., 2004). It has even been reported in a clinical study that the loss of 10% of weight significantly decreases the markers of oxidative damage to DNA (Hofer et al., 2008).

### 4.2 | Hypertension, oxidative stress, and inflammation

In animal models the importance of oxidative stress in the development of hypertension has been demonstrated (Larsen & Matchkov, 2016). Clinical studies with subjects with essential hypertension, positive correlation between blood pressure with markers of oxidative stress, and negative correlation with the concentration of antioxidant enzymes was found (Larsen & Matchkov, 2016).

The decrease in the bioavailability of nitric oxide is one of the key factors in hypertension. Calcium-mediated activation of the endothelial nitric oxide synthase (eNOS) leads to the production of nitric oxide (NO) which diffuses from the endothelial cells to the vascular smooth muscle cells where it leads to the vasodilation lowering total peripheral resistance and blood pressure (Vanhoutte, Shimokawa, Tang, & Feletou, 2009).

The excessive production of reactive oxygen species, particularly superoxide anion ($O_2^{-\cdot}$), from different routes, decreases the availability of nitric oxide, which causes vasoconstriction (Larsen & Matchkov, 2016).

### 4.3 | Hypertriglyceridemia and oxidative stress

Hypertriglyceridemia has been associated with oxidative stress (Rehman & Akash, 2017). A direct correlation has been reported between the high concentration of triglycerides and 8-hydroxyguanine (8-OH-dG) (Ferri et al., 2008). A higher concentration of oxidized glutathione has also been evidenced in hyperlipidaemic patients (Martínez-Hervás et al., 2008).

### 4.4 | Diabetes mellitus type 2, oxidative stress, and inflammation

There is ample evidence of the relationship between oxidative stress and DM2. Clinical studies in patients with DM2 demonstrate higher concentrations of pro-oxidants and biomarkers of tissue damage induced by oxidative stress (such as oxidation of DNA bases). It has been reported that 4-hydroxy-2-nonenal proteins (HNE), hydroperoxides, 8-OH-dG and 8-epi-prostaglandin (F2α) are elevated in people with DM2 (Sakuraba et al., 2002; Shin et al., 2001). It has also been shown that the total antioxidant status (TAS), as well as the enzymatic antioxidant components (such as glutathione peroxidase, catalase, and superoxide dismutase) and nonenzymatic (such as vitamin C and E) decrease in DM2 (Demircan et al., 2008; Ford, Mokdad, Giles, & Brown, 2003), while the levels of peroxides and other biomarkers of oxidative stress increase significantly (Demircan et al., 2008). In another study, it was found that people with DM2 had lower concentrations of the reduced glutathione (GSH) and higher concentrations of oxidized glutathione (GSSG) (Murakami et al., 1989).

There is evidence that people with DM2 have higher concentrations of oxidative damage and that it correlates with glycaemic control, higher concentration of plasma nitrotyrosine, oxidized LDL, 8-OH-dG in mononuclear cells, and urine (Roberts & Sindhu, 2009).

## 5 | RANDOMIZED CONTROLLED CLINICAL TRIALS ON DIET AND MARKERS OF OXIDATIVE STRESS IN SUBJECTS WITH METABOLIC DISEASES

All randomized controlled intervention trials (RCTs) published in MEDLINE (U.S. National Library of Medicine, National Institutes of Health) considered met the following criteria: (a) adult subjects affected by metabolic diseases (obesity, hypertension, diabetes, or dyslipidemia); (b) intervention in the diet (food supplements, powders, and common foods or beverages); (c) evaluation of oxidative stress with validated biomarkers in vivo (Table 1); (d) published in the last 5 years.

### 5.1 | Diet and oxidative stress in overweight or obese subjects

The Dietary Approaches to Stop Hypertension (DASH) is characterized by a high amount of fruits and vegetables, with low consumption of dairy products. A hypocaloric diet for 8 weeks decreased biomarkers of oxidative stress (Asemi et al., 2014), which can be attributed to its high content of fruits and vegetables rich in antioxidants, since individuals in the DASH group received twice as much vitamin C as the control group. The consumption of vegetables and legumes increases the total antioxidant capacity and this effect seems to be

greater when an amount of folate is consumed close to the Dietary Reference Intake (DRI) (Ataíde-Lima et al., 2017).

The consumption of 37 mg of lycopene contained in tomato juice for 20 days, increased the total antioxidant capacity and the enzymes SOD, CAT, and GPx in erythrocytes, accompanied by a decrease in MDA (Ghavipour, Sotoudeh, & Ghorbani, 2015). In another similar study, but with a higher content of lycopene (60mg), no differences were found on TAC, SOD, CAT, or GPx (Pourahmadi, Mahboob, Saedisomeolia, & Reykandeh, 2015). The study by Ghavipour et al. (2015) found changes in the antioxidant capacity in overweight people, but not in people with obesity, so it is possible that the effect of lycopene depends on the dose and the metabolic state of the person.

Some studies with different dietary treatments (pomegranate juice, symbiotic, cocoa) that improve markers of oxidative stress, have in common a decrease in body weight, as described below.

Supplementation with 1g of pomegranate juice extract for 30 days, decreased the concentration of MDA and IL-6 and C-reactive protein (Hosseini, Saedisomeolia, Wood, Yaseri, & Tavasoli, 2016), related to a greater reduction in body weight. It has been reported that pomegranate juice decreases the absorption of lipids (Lei et al., 2007), decreases appetite, and increases the production of adiponectin (Guo et al., 2008), which can cause weight loss.

The consumption of 32.27 mg of polyphenols contained in cocoa extract during 4 weeks, had no effect on the level of oxidative damage in the DNA. However, when the volunteers of both groups were analyzed together, a marginal decrease was observed in the oxidized bases, which was attributed to weight loss. Moreover, the subjects who started the intervention with higher levels of damage had a greater reduction of the oxidized bases after 4 weeks, in comparison with those who had lower initial levels (Ibero-Baraibar, Azqueta, López, Martínez, & Zulet, 2015).

It has been reported that the weight reduction ≥5%, maintained for 1 year and caused by hypocaloric diet (1,200–2,000 kcal/day) alone or in combination with aerobic exercise (45 min, 4 metabolic equivalents [METs], 70%–85% heart rate, 5 days a week) decreased some lipid markers of oxidative stress (oxidized LDL and F2-isoprostanes), although it increased fluorescent oxidation products (Duggan et al., 2016).

In contrast, the consumption of foods rich in antioxidants in the absence of weight loss may not be enough to modify markers of oxidative stress, as shown by a study where subjects consumed 42.5 g of almonds and/or cocoa (18 g powder and 43 g of dark chocolate) for 4 weeks and had no effect on LDL resistance to oxidation or urinary excretion of isoprostanes (Lee et al., 2017). In another study in subjects without dyslipidaemias (total cholesterol, c-LDL, c-HDL, and triglycerides within normal parameters) normotensive, normoglycemic although with BMI 20–35 kg/m$^2$, consuming 3 or 5 cups of coffee for 5 weeks did not decrease DNA damage, urinary excretion of isoprostanes, or C-reactive protein or IL-6 (Shaposhnikov et al., 2016).

These studies seem to indicate that weight reduction is an important factor in improving the redox state. However, some effects remain even when the results are adjusted for confusing variables such as weight loss and diet, as demonstrated by a study with oil *Nigella sativa* whose consumption for 8 weeks increased the activity of red cell SOD, although it had no effect on GPx, TAC, or MDA, where the effect remained after adjusting for weight loss, diet, and baseline values (Namazi, Mahdavi, Alizadeh, & Farajnia, 2015).

The mechanisms of antioxidant action of dietary interventions with fruits and vegetables may be due to several reasons: high content of vitamins, minerals, and bioactive compounds with antioxidant capacity; some vitamins are required as coenzymes in DNA repair processes; the minerals act as enzymatic cofactors of the enzymes of the antioxidant system; fiber can reduce glucose absorption, avoiding postpublic hyperglycaemia that increases the production of reactive species (Vetrani, Costabile, Di Marino, & Rivellese, 2012). On the other hand, the loss of adipose tissue may favor an anti-inflammatory state and reduce oxidative stress (Bays, Blonde, & Rosenson, 2006). Table 2 summarizes the studies mentioned above.

## 5.2 | Diet and oxidative stress in subjects with dyslipidaemia

There are few randomized controlled clinical studies conducted in subjects with dyslipidaemia, published in the last 5 years where the effect of diet on markers of oxidative stress was evaluated. In most of them, in addition to dyslipidaemia, subjects with overweight or obesity were included (Table 3).

Some of the studies evaluated the antioxidant capacity of plasma, after treatment with a food with a known amount of polyphenols derived from orange juice, bran oil, or grapes, resulted an increase in plasma antioxidant capacity (Bumrungpert, Chongsuwat, Phosat, & Butacnum, 2018; Constans et al., 2015; Rahbar, Mahmoudabadi, & Islam, 2015).

The consumption of 212 mg/day of hesperidin in orange juice during 4 weeks in men with hypercholesterolemia, increased the plasma antioxidant capacity, accompanied by a decrease in the urinary excretion of isoprostanes; however, the activity of erythrocyte CAT decreased. These results may be due to the direct effect of ascorbic acid and polyphenols contained in the juice, which increased in plasma significantly (Constans et al., 2015).

The administration of different doses of gamma-oryzanol contained in rice bran oil in subjects with high LDL-C for 4 weeks, increased the plasma antioxidant capacity. This effect was achieved with 400 ppm or 8,000 ppm/day (Bumrungpert et al., 2018).

The consumption of 500 g/day of red or white grapes in people with hypercholesterolemia during 4 weeks, decreased the concentration of MDA and increased TAC. Although both varieties of grapes had this effect, the decrease in MDA was greater in the group that consumed red grapes, which can be attributed to a higher content of polyphenols (0.652 versus 0.598 mg/g dry weight) (Rahbar et al., 2015).

Other studies with seeds have also been reported however, its content of bioactive compounds was not determined. In the first one, the

**TABLE 2** Randomized controlled clinical studies on diet and markers of oxidative stress in overweight or obese subjects

| Reference | Subjects | Study design | Oxidative stress marker | Results |
|---|---|---|---|---|
| Asemi et al. (2014) | *n* = 48 women (18–40 years) Polycystic ovary, BMI ≥ 25 kg/m$^2$ | Parallel groups (8 weeks)<br>Hypocaloric diet: 52% carbohydrates, 18% proteins and 30% fat.<br>1. Control diet.<br>2. 2. DASH diet. | Plasma plasma<br>GSH | ↑ TAC<br>↑ GSH |
| Ataíde-Lima et al. (2017) | *n* = 40 women (20–59 years)<br>BMI 25–35 kg/m$^2$ | Parallel groups (8 weeks)<br>1. 300 g of vegetables and legumes with 191 μg/day of folate + hazelnut oil<br>2. 300 g of vegetables and legumes with 191 μg/day of folate + placebo<br>3. 300 g of vegetables and legumes with 90 μg/day of folate + hazelnut oil<br>4. Diet usual | serum TAC<br>plasma MDA | ↑ CT in groups a and b |
| Duggan et al. (2016) | *n* = 439 women (50–75 years)<br>BMI ≥ 25 kg/m$^2$ | Parallel groups (12 months)<br>1. Hypocaloric diet<br>2. Moderate-intense aerobic exercise<br>3. Diet + Exercise<br>4. Control | Plasma FOP<br>ox-LDL serum<br>F2α-isoprostanes plasma | ↓ F2α-isoprostanes in diet, exercise and diet + exercise groups.<br>↓ ox-LDL in groups, diet and diet + exercise.<br>↑ FOP in groups, diet and diet + exercise.<br>Weight reduction was associated with the reduction of oxidized LDL and F2-isoprostanes, as well as the increase in FOP |
| Ghavipouret al. (2015) | *n* = 64 women (20–30 years)<br>BMI ≥ 25 kg/m$^2$ | Parallel groups (20 days)<br>1. Control<br>2. 330 ml of tomato juice per day, with a lycopene content of 37 mg. | Plasma<br>TGA serum MDA<br>GPx erythrocyte<br>CAT erythrocyte<br>SOD erythrocyte | ↑ TAC, GPx, CAT, SOD in overweight people, but not with obesity<br>↓ MDA in overweight people, but not with obesity |
| Pourahmadi et al., 2015 | *n* = 75 women (20–30 years)<br>BMI ≥ 25 kg/m$^2$ | Parallel groups (20 days)<br>1. Control<br>2. 330 ml of tomato juice, with a lycopene content of 60 mg | TAC<br>CAT<br>GPx<br>SOD | No change |

(Continues)

**TABLE 2** (Continued)

| Reference | Subjects | Study design | Oxidative stress marker | Results |
|---|---|---|---|---|
| Hosseini et al., 2016 | *n* = 48 people (30– 60 years)<br>BMI ≥ 25 kg/ $m^2$ (overweight) and < 40 kg/$m^2$ (obesity) | Parallel groups (30 days)<br>1. Placebo<br>2. 1 g of pomegranate extract (whole fruit with 40% ellagic acid) | plasma | ↓ MDA |
| Ibero-Baraibar et al., 2014 | *n* = 50 people ( 50–80 years)<br>BMI = 27–35.5 kg/$m^2$ | Parallel groups (4 weeks). Hypocaloric diet (15%)<br>1. Control<br>2. 1.4 g/ day of cocoa extract with 32.27 mg of total polyphenols | Comet assay in lymphocytes<br>Oxidized bases in lymphocytes | No changes in DNA<br>Negative correlation between oxidized bases and epicatechin-O-sulfate and methyl-epicatequina-O-sulfato |
| Lee et al. (2017) | *n* = 31 people (30–70 years)<br>BMI = 25–40 kg/$m^2$<br>c-LDL percentile 25–95 NHNES 1999–2000 | Crusader, 4 periods (4 weeks each period and 2 weeks washing period). Isocaloric diet<br>Average American diet42.5 g/ day almonds18 g/day cocoa powder and 43 g/ day dark chocolatealmonds + cocoa +chocolate | Resistance of LDL to oxidation LDL ex vivo<br>$F_{2\alpha}$- urinary isoprostanes | No change |
| Namazi et al., 2015 | *n* = 49 women (25–50 years)<br>BMI = 25–40 kg/$m^2$ | Parallel groups (8 weeks). Hypocaloric diet<br>Capsules with sunflower oil as a placebo<br>Capsules with 3 g/day of oil *Nigella sativa* | SOD erythrocyte<br>GPx erythrocyte<br>serum TAC serum<br>MDA | ↑ SOD<br>No change GPx, TAC, MDA |

**TABLE 3** Randomized controlled clinical studies on diet and markers of oxidative stress in subjects with dyslipidaemia

| Reference | Subjects | Study design | Oxidative stress marker | results |
|---|---|---|---|---|
| Bento et al. (2014) | *n* = 25 people (21–57 years)<br>BMI: 18.5 –29.99 kg/m$^2$<br>Hypercholesterolemia mild (5.2–7.3 mmol/L) | crossed, 2 periods (6 weeks each period and 4 weeks' washout period). Without modification in diet or physical activity<br>1. 20 g/day almonds baru<br>2. 20 g/day corn starch as placebo | plasma SOD plasma<br>MDA<br>FRAP | unchanged |
| Constans et al. (2015) | *n* = 25 men (50–60 years)<br>c-LDL = 130–190 mg/dl | Crossed, 2 periods (4 weeks each period and 5 weeks washing period)<br>1. 200 ml juice without citrus fruits<br>2. 200 ml orange juice with 212 mg/day of hesperidin | GPx erythrocyte<br>SOD erythrocyte<br>CAT erythrocyte<br>F2α-isoprostanes urinary<br>plasma ORAC plasmatic<br>FRAP | ↑ FRAP and ORAC<br>↓ CAT, F2α-isoprostanes<br>GPx and SOD unchanged |
| Bumrungpert et al. (2018) | *n* = 59 people (20–60 years)<br>LDL-C > 100 mg/dl | Parallel groups (4 weeks)<br>1. Soybean oil as control<br>2. 4,000 ppm gamma-oryzanol in bran oil rice<br>3. 8,000 ppm of gamma-oryzanol in rice bran oil<br>4. 11.000 ppm of gamma oryzanol in-rice bran oil | ORAC<br>FRAP | ↑ FRAP and ORAC |
| Rahbar et al. (2015) | *n* = 61 persons (20–70 years)<br>BMI = 19.8–35 kg/m$^2$<br>Hypercholesterolemia ≥ 200 mg/dl | Parallel groups (8 weeks)<br>1. Control<br>2. 500 g/day Condori red grapes<br>3. 500 g/day white grapes Shahroodi | plasma MDA Plasma<br>TAC | ↑ TAC both groups<br>↓ MDA both groups, greater effect on red grapes. |
| Lee et al. (2016) | *n* = 53 people (> 30 years<br>BMI = 23–30 kg/m$^2$<br>c-LDL = 130–165 mg/dl | Parallel groups (8 weeks)<br>1. 80 ml/day of drink with 13.5 g of wolfberry<br>2. 80 ml/day placebo drink | SOD erythrocyte erythrocyte<br>CAT erythrocyte<br>GPx<br>plasma oxDA-LDL Plasma<br>MDA<br>DNA damage in lymphocytes (comet assay)<br>SOD mRNA, TXNRD1 | ↓ SOD and DNA damage<br>↑ CAT<br>GPx, oxLDL and MDA unchanged<br>↓ mRNA SOD, TXNRD1 |

consumption of 20 grams of Baru almonds in subjects with hypercholesterolemia for 6 weeks had no effect on SOD, MDA, or TAC (Bento, Cominetti, Filho, & Naves, 2014). In the second, the administration of a drink with 13.5 g of Goji berries (Wolfberry) during 8 weeks decreased the oxidative damage in the DNA and increased the activity of erythrocyte CAT; however, it decreased the expression of SOD mRNA and its activity; this drink also decreased the expression of toll-like receptors 4 (TLR 4), TNF, and IL-6, suggesting an anti-inflammatory effect (Lee et al., 2016).

It should be noted that the increase in antioxidant activity may not be mediated by an increase in enzymatic activity (Constans et al., 2015; Lee et al., 2016) since, as mentioned above, some bioactive compounds present in food have direct antioxidant activity.

### 5.3 | Diet and oxidative stress in subjects with hypertension

As in the case of studies with dyslipidaemia, few clinical studies were found in people with hypertension. Of the reports found (Table 4), no conclusive results were found with the treatment with Brazil nut, lyophilized berries, extra virgin olive oil, or spirulina (Huguenin et al., 2015; Jhonson et al., 2017; Martínez-Sámano, Torres-Mones de Oca, Luqueño-Bocardo, Torres-Durán, & Juárez-Oropeza, 2018; Storniolo et al., 2015).

Supplementation with 13 g of Brazil nut for 12 weeks increased the plasma GPx activity, but had no effect on TAC or markers of oxidative damage 8-epi $PGF_{2\alpha}$ and oxLDL (Huguenin et al., 2015).

The consumption of lyophilized berry powder for 8 weeks, decreased the marker of damage to the DNA 8-OH-dG, but only at week 4, which suggests an acute effect that does not prevail with time. Other markers of oxidative stress (SOD, GR, GPx, 8-isoprostane, MDA) did not show differences (Jhonson et al., 2017).

**TABLE 4** Randomized controlled clinical studies on diet and markers of oxidative stress in subjects with hypertension

| Reference | Subjects | Study design | Oxidative stress marker | Results |
|---|---|---|---|---|
| Huguenin et al. (2015) | *n* = 91 people (>20 years) | Crusader, 2 periods (12 weeks each period and 4 weeks washout period) | Plasma GPx plasma | ↑ GPx |
| | Diagnosis and pharmacological treatment of dyslipidemia and hypertension | | TAC | |
| | | 1. Placebo<br>2. 13 g/ day of defatted Brazil nut, with 227.5 μg of Selenium | 8-epi $PGF_{2\alpha}$ plasma ox-LDL plasma | 8 -epi $PGF_{2\alpha}$, TAC and ox-LDL without change<br>Reverse association between the activity of GPx and ox-LDL, simple model and adjusted for age, BMI, sex, diabetes and smoking |
| Jhonson et al. (2017) | *n* = 40 women (45–65 years old) | Parallel groups (8 weeks) | 8-OHdG | ↓ 8- OHdG at 4 but not at 8 weeks. |
| | Pre-hypertension stage 1 | | serum SOD serum | |
| | | 1. Placebo<br>2. 22 g of blueberry lyophilized powder (equivalent to 1 cup of fresh fruit) | MDA<br>8-epi $PGF_{2\alpha}$<br>plasmaticGPx<br>plasmaGR<br>Ox-LDL | SOD, GR, GPx, 8-epi $PGF_{2\alpha}$, MDA without change |
| Martínez-Sámano et al. (2018) | *n* = 16 people | Parallel groups (12 weeks) | plasma CAT | ↑ GPx, SOD and GSSG |
| | Systemic arterial hypertension | | SOD plasma | |
| | Treatment with ACE inhibitor | 1. Placebo<br>2. 4.5 g/day of *Spirulina maxima* | GPx plasma<br>GR plasma<br>GSH plasma<br>GSSG plasma<br>plasma MDA | CAT, GR,<br>GSH and MDA unchanged |
| Storniolo et al. (2015) | *n* = 90 women (60 –80 years) | Parallel groups (1 year) | MDA | No changes |
| | With cardiovascular risk: DM, hypertension (≥10/85 mmHg), LDL-C (≥160 mg/dl, c-HDL ≤ 42 mg/dl), BMI ≥ 25 $kg/m^2$ or family history of cardiovascular disease | 1. Control low in fat (40 g/ d olive oil)<br>2. TMB + extra virgin olive oil (52 g/day)<br>3. TMB + nuts (7.5 g/d hazelnuts, 7.5 g/d almonds) and 40 g/d olive oil | TAC | |

Abbreviations: ECA, Angiotensin Converting Enzyme; TMB, Mediterranean traditional diet.

Treatment with 4.5 g/day of Spirulina for 12 weeks increased the activity of GPx and SOD; an increase in the oxidized form of glutathione was also found, which may be due to the activity of GPx; other antioxidant enzymes (CAT, GR) as well as the lipid oxidative damage marker MDA did not differ (Martínez-Sámano et al., 2018; Storniolo et al., 2015).

A study conducted in women during a year with cardiovascular risk found no effect of the consumption of 15 g of walnuts or

**TABLE 5** Randomized controlled clinical studies on diet and markers of oxidative stress in subjects with type 2 diabetes

| Reference | Subjects | Study design | Oxidative stress marker | Results |
|---|---|---|---|---|
| Atkin et al. (2016) | *n* = 26 people (18–70 years) at high risk of cardiovascular event (30%) | Crusader, 2 periods (4 weeks each period and 4 weeks washout period) | plasma TAOS | No change |
| | | | GSH/GSSG erythrocyte | |
| | | 1. 1,200 mg of aged garlic extract<br>2. Placebo | plasma LHP | |
| Derosa et al. (2016) | *n* = 105 people (18–75 years) | Parallel groups (3 months) | SOD | ↑ SOD and GPx |
| | $HbA_{1c}$ > 7% | | GPx | |
| | BMI: 25–30 kg/m$^2$ | 1. 600 mg of α-lipoic acid, 165 mg of L-carnosine, 7.5 mg of zinc, 9 mg $B_3$, 3 mg $B_5$, 1 mg $B_6$, 0.7 mg $B_1$, 0.8 mg $B_2$, 0.5 µg $B_{12}$, 100 µg folic acid<br>2. Placebo | MDA | ↓ MDA |
| Ebrahimpour al. (2015) | *n* = 40 (25–50 years) | Parallel groups (45 days). | Erythrocyte SOD | ↑ SOD, GPx and TAC |
| | DM2 > 6 months | | GPx erythrocyte | |
| | | 1. Placebo<br>2. 140 mg dry extract *Silybum marianum*, 3 times a day. | serum TAC Serum | ↓ MDA |
| | | | MDA | |
| Homayouni et al. (2017) | *n* = 64 people (30–65 years) | Parallel groups (6 weeks). | serum TAC | ↑ TAC |
| | DM2 > 3 years | | 8-OH-dG serum | |
| | BMI < 30 kg/m$^2$ | 1. Placebo<br>2. 500 mg/day of hesperidin | MDA serum | ↓ MDA and 8-OH-dG |
| Karimi et al. (2015) | *n* = 56 women (30–65 years) | Parallel groups (8 weeks). | MDA | ↑ TAC |
| | DM2 > 6 months | | TAC | ↓ MDA |
| | BMI > 25 kg/m$^2$ | | SOD | SOD, GPx and CAT without changes |
| | | 1. Maltodextrin as placebo<br>2. 10 g/day resistant starch type 5 | CAT | |
| | | | GPx | |
| Mirmiran et al. (2017) | *n* = 40 people (50–75 years) | Cross groups, 2 periods (8 weeks each period and 4 weeks washing period) Diet: 50%–60% carbohydrates, 15% proteins and 25%–35% fat | Serum MDA Serum | ↑ CAT |
| | BMI = 25–30 kg/m$^2$ | | TAC | |
| | | 1. Free of legumes<br>2. With legumes, not soy. | ox-plasma LDL | ↓ MDA, ox-LDL |
| | | | CAT | TAC unchanged |
| Sohrab et al. (2016) | *n* = 62 (40–65 years) | Parallel groups (6 months). | serum ox LDL | ↓ ox-LDL |
| | DM2 > 12 months | 1. Control<br>2. 200 ml/day of Pomegranate Juice, with a content of 2.125 g/L of polyphenols and 385 µg/ml of flavonoids. | | |
| Takahashi et al. (2014) | *n* = 22 women (62–73 years) | Parallel groups (4 weeks). | d-ROM serum | ↑ TRX only postprandial. |
| | DM > 3 months | 1. Drink with 92 mg/350 ml of catechins as a placebo.<br>2. Drink with 615 mg/350 ml of catechins) | $H_2O_2$ plasmatic plasma | d-ROM and $H_2O_2$ unchanged |
| | | | TRX | |

52 g of extra virgin olive oil on MDA and total antioxidant capacity (Storniolo et al., 2015). It should be noted that all groups consumed traditional Mediterranean diet and it is possible that, although it is supplemented with nuts or oil with a greater amount of polyphenols such as extra virgin, it does not represent a greater benefit than that achieved by the diet.

In this regard, a previous study showed that the consumption of olive oil (366 mg polyphenols/kg of oil) decreased the concentrations of isoprostanes and 8-OH-dG (Cicero et al., 2008). In addition, the Mediterranean diet is one of the most recommended dietary patterns for the prevention of chronic degenerative diseases. The ATTICA study showed a negative association between the Mediterranean diet and lipid peroxidation (Panagiotakos, Pitsavos, Chrysohoou, Skoumas, & Stefanadis, 2004). However, other controlled, randomized clinical studies have not confirmed this association (Vetrani et al., 2012).

### 5.4 | Diet and oxidative stress in subjects with diabetes mellitus type 2

Consumption of green tea with a high catechin content for 6 weeks did not decrease the peroxide content and only increased postprandial thioredoxin activity, but no effects were found after treatment (Takahashi et al., 2014). Moreover, the consumption of 200 ml of pomegranate juice with 2,125 mg/L polyphenols and 385 μg/ml of flavonoids, for 6 months, decreased the concentration of oxidized LDL (Sohrab et al., 2016). Supplementation with 500-mg hesperidin for 6 weeks, increased TAC and decreased the markers of damage 6-OHDA and MDA; this difference was significant with respect to the baseline status, control group and after adjusting for age, duration of DM, BMI, diet, and physical activity (Homayouni, Haidari, Hedayati, Zakerkish, & Ahmadi, 2017).

Considering that the dose of catechins and hesperidin in two studies were similar, while the flavonoids in pomegranate juice had a lower dose but a higher amount of polyphenols, it is likely that the discrepancies were due to the dose and type of polyphenols present. Regarding green tea, previous reports in subjects with hypertension (Hogdson et al., 2002), moderate hypercholesterolemia (Davies et al., 2003; Hogdson et al., 2002), or type 2 diabetes (Neyestani et al., 2010) seem to have no significant effect, unlike healthy subjects, where it has been shown that oxidative damage to DNA decreases (van het hoff et al., 1997).

The studies where the content of bioactive compounds is not reported represents a limitation since it does not allow comparing them with other reports or inferring the mechanisms of action. Such is the case of the treatment with garlic extract aged for 4 weeks, which did not modify the plasma antioxidant status, the proportion of oxidized/reduced glutathione nor the oxidative damage in lipids (Atkin, Laight, & Cummings, 2016). In contrast, the consumption of milk thistle extract (*Silybum marianum*) during 45 days, increased the activity of SOD, GPx, and total antioxidant capacity, with decreased MDA (Ebrahimpour, Gargari, Mobasseri, Valizadeh, & Ashgari Jafarabadi, 2015).

In this same sense, the treatment with supplements that contain a mixture of nutrients does not allow us to discern which of them had the effect. The administration of a supplement with lipoic acid, B-complex vitamins, zinc, and carnosine for 3 months increased the activity of SOD, GPx, with the reduction of MDA (Derosa, D'Angelo, Romano, & Maffioli, 2016).

The substitution of foods and the incorporation of dietary fiber, seem to improve the redox state as shown by two studies. A diet with the same distribution of macronutrients, where 2 portions of meat were replaced by legumes (different from soy) for 8 weeks, decreased markers of MDA and ox-LDL damage, and increased CAT activity (Mirmiran, Hosseinpour-Niazi, & Azizi, 2017). The consumption of 10 g of resistant starch during 8 weeks, increased TAC and decreased MDA; however, no changes were found in SOD and CAT (Karimi et al., 2015). It is probable that the microbiota has an important role in the redox state since it is known that the resistant starch favors the proliferation of microbiota with anti-inflammatory capacity (Yang et al., 2017).

The summary of these studies is presented in Table 5.

Finally, an important element of lifestyle is the practice of physical activity and there are clinical, controlled, randomized studies that evaluate the joint effect of diet with exercise. No studies were found where only the effect of exercise on markers of oxidative stress in subjects with chronic diseases such as obesity, hypertension, diabetes, and dyslipidaemias in the last 5 years was evaluated. However, a clinical study conducted in 24 sedentary women (30–55 years) who performed moderate aerobic exercise (75% maximum heart rate), for 6 weeks (50 min, 3 days a week), reported an increase in antioxidant capacity and decrease of malondialdehyde, although without change of plasmatic hydroperoxide (Leelarungrayub et al., 2011).

It is known that physical activity decreases the risk of mortality, as well as the risk of diabetes and cardiovascular diseases. The evidence suggests that the mechanism of action is the anti-inflammatory effect of exercise, which increases IL-6, IL-10, and IL1ra, which inhibit the production of TNF-α and IL-1β (Pedersen, 2017). On the other hand, exercise decreases abdominal adiposity, which ultimately also has an anti-inflammatory effect. However, in clinical practice, it is important to select the appropriate intensity, duration, frequency, and type of exercise, which decrease the EO markers and/or inflammation.

## 6 | CONCLUSIONS

Although some studies showed no effect of diet on the oxidative state, there was vast evidence that changes in diet may influence the redox status in overweight or obese subjects, hypertension, diabetes, or dyslipidaemias. This effect on the redox state can be directly on the total capacity (TAC, TOS, FRAP, ORAC), which can be explained by the presence of nutrients with antioxidant capacity such

as polyphenols or bioactive compounds in certain foods. However, certain changes in the diet such as: the decrease in the caloric content with or without exercise, but which leads to weight loss; Isocaloric diets with substitution of animal protein by vegetable protein, and incorporation of fiber, can increase the activity of enzymatic antioxidants such as GSH, GPx, CAT, SOD, and TRX, where the loss of adipose tissue, anti-inflammatory capacity, and changes in the microbiota may be the mechanisms involved. Further clinical, controlled, and randomized studies evaluating the effect of exercise on EO markers in subjects with chronic diseases are necessary. They should consider an analysis adjusted to confusing variables, such as weight loss and baseline status, exploring the mechanisms of action involved.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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