

2015

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REVIEW ARTICLE

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Obesity-Related Oxidative Stress: the Impact of Physical Activity and Diet Manipulation

Chun-Jung Huang^{1*}, Matthew J. McAllister², Aaron L. Slusher^{1,3}, Heather E. Webb⁴, J. Thomas Mock¹ and Edmund O. Acevedo³

Abstract

Obesity-related oxidative stress, the imbalance between pro-oxidants and antioxidants (e.g., nitric oxide), has been linked to metabolic and cardiovascular disease, including endothelial dysfunction and atherosclerosis. Reactive oxygen species (ROS) are essential for physiological functions including gene expression, cellular growth, infection defense, and modulating endothelial function. However, elevated ROS and/or diminished antioxidant capacity leading to oxidative stress can lead to dysfunction. Physical activity also results in an acute state of oxidative stress. However, it is likely that chronic physical activity provides a stimulus for favorable oxidative adaptations and enhanced physiological performance and physical health, although distinct responses between aerobic and anaerobic activities warrant further investigation. Studies support the benefits of dietary modification as well as exercise interventions in alleviating oxidative stress susceptibility. Since obese individuals tend to demonstrate elevated markers of oxidative stress, the implications for this population are significant. Therefore, in this review our aim is to discuss (i) the role of oxidative stress and inflammation as associated with obesity-related diseases, (ii) the potential concerns and benefits of exercise-mediated oxidative stress, and (iii) the advantageous role of dietary modification, including acute or chronic caloric restriction and vitamin D supplementation.

Key Points

- Acute exercise is a small source of oxidative stress, while chronic exercise elicits protective adaptations against oxidative damage.
- Chronic ingestion of energy-rich foods may contribute to obesity, while acute ingestion may also elicit potentially adverse metabolic responses including oxidative stress.
- Caloric restriction may attenuate oxidative stress and serve as a beneficial weight loss intervention for obese individuals.

Review

Introduction

The prevalence of obesity continues to increase in the USA, with recent reports indicating over 64.1 % of American women and 72.3 % of American men are

categorized as overweight and/or obese [body mass index (BMI) ≥ 25 kg/m²] [1]. Obese individuals have demonstrated markers indicative of oxidative stress, including elevated measures of reactive oxygen species (ROS) [2] and diminished antioxidant defense, which is associated with lower antioxidant enzymes [3]. Oxidative stress is associated with systemic inflammation, endothelial cell proliferation and apoptosis, and increased vasoconstriction, and thus a noteworthy contributing factor to endothelial dysfunction. In concert, this evidence supports the relationship between oxidative stress, endothelial dysfunction, atherosclerosis, and cardiovascular disease (CVD) [4].

Oxidative stress is a general term for cellular damage caused by an imbalance between pro-oxidants such as ROS and/or reactive nitrogen species (RNS) antioxidants. ROS are oxidizing agents generated during cellular metabolism when the chemical reduction of oxygen forms unstable free radicals, characterized by an unpaired electron [4]. ROS are essential for physiological functions such as gene expression, cellular growth, infection defense, and modulating endothelial function

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[4–6]. However, to maintain a physiologically beneficial level of ROS within cells, antioxidants are necessary. Antioxidants are enzymatic and nonenzymatic molecules which significantly delay or prevent the oxidizing damage of ROS through the inhibition of ROS formation and action or by repairing cells which have been damaged by ROS [5].

Furthermore, obesity-induced inflammation is frequently associated with increased oxidative stress (Fig. 1). Specifically, leptin, an adipocyte-derived hormone, is elevated in obese individuals and can induce oxidative stress [7] and plays a key role in mediating a pro-inflammatory state in obesity [8]; and Korda et al. [7] indicated that this physiological link may help to explain the relationship of obesity, oxidative stress, and inflammation. Additionally, the chronic ingestion of lipid-rich meals can also enhance oxidative stress, lead to weight gain, and facilitate the development of insulin resistance [9]. These negative effects can be attenuated with specific nutrient intake strategies including caloric restriction (CR) and the consumption of exogenous antioxidants. Finally, oxidative stress is elevated during physical activity, but likely serves to instigate a positive antioxidant adaptation [10, 11]. In this review, MEDLINE and PUBMED records were searched using the terms obesity, oxidative stress, inflammation, exercise/physical activity, diets, and antioxidants to identify the studies published in the past 10 years pertaining to two

factors that impact obesity-related oxidative stress: physical activity intervention and diet manipulation. Therefore, in this review our aim is to discuss (i) the role of oxidative stress and inflammation as associated with obesity-related diseases, (ii) the potential concerns and benefits of exercise-mediated oxidative stress, and (iii) the advantageous role of dietary modification, including acute or chronic CR and vitamin D supplementation.

Obesity: a Link between Oxidative Stress and Inflammation

One of the earliest subclinical stages in the atherosclerotic process is an impairment of endothelium-dependent vasodilation, also known as endothelial dysfunction [12]. A mediator of obesity-induced endothelial dysfunction is the level of oxidative stress. Oxidative stress is an imbalance between antioxidants [e.g., superoxide dismutase (SOD) and glutathione peroxidase (GPX)] and reactive oxygen species [e.g., superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-)] [13]. Under normal physiological conditions, nitric oxide (NO) is a critical homeostatic regulator of the vessel wall and plays a role in the maintenance of vascular tone and reactivity [14]. However, when ROS production is elevated, the process of cell damage occurs and can possibly facilitate the development of CVD [15] which is largely attributed to oxidation of low-density lipoprotein (LDL) [16]. Several

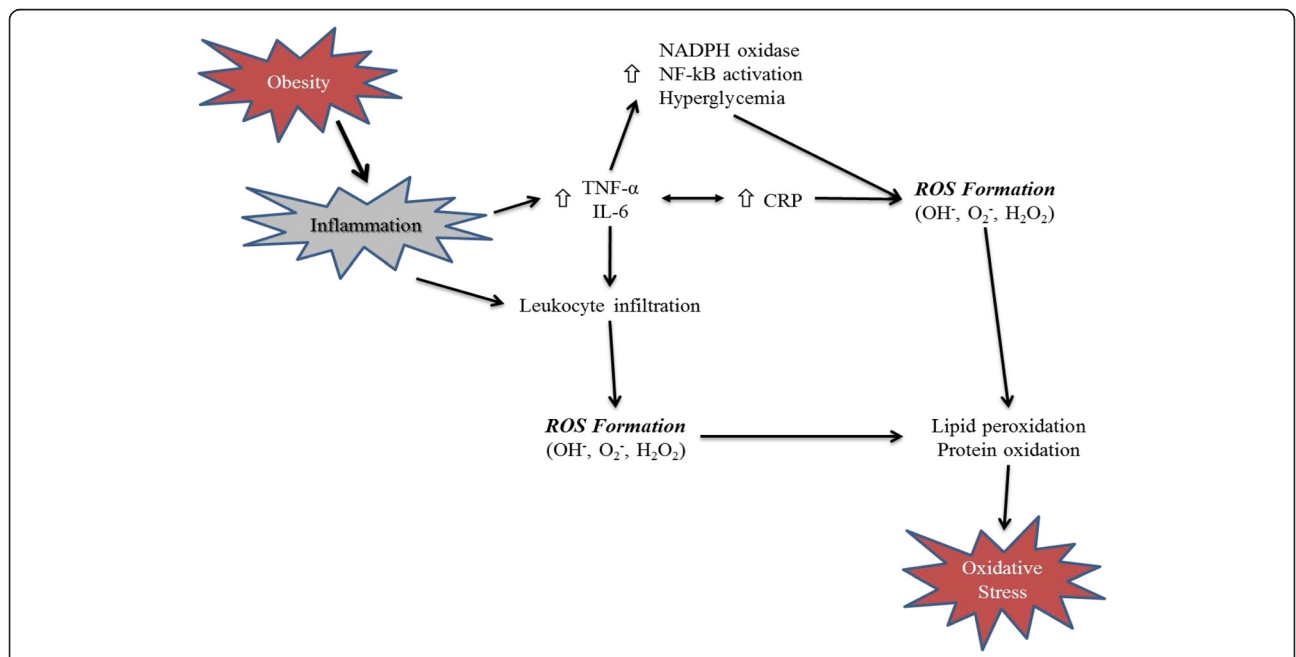


Fig. 1 The link between obesity-induced inflammation and oxidative stress. Increased pro-inflammatory response and leukocyte infiltration in obese populations promote the formation of ROS, resulting in oxidative stress. *NADPH* nicotinamide adenine dinucleotide phosphate, *NF-kB* nuclear factor kappa B, *TNF-α* tumor necrosis factor, *IL-6* interleukin-6, *CRP*, C-reactive protein, *OH·*, hydroxyl radical, *O²⁻* superoxide, *H₂O₂* hydrogen peroxide, *ROS* reactive oxygen species

oxidative enzymes such as myeloperoxidase (MPO) and lipoxygenases have been shown to involve in LDL oxidation [17, 18] and are associated with the development of obesity along with inflammation and insulin resistance [19, 20]. Furthermore, increased endogenous activity of antioxidants such as SOD and GPX can decrease the potential for CVD development by regulating ROS and NO production [21, 22]. Importantly, the vascular response to shear stress in obese individuals has been shown to be attenuated [23]. This subsequent attenuation of shear stress has been shown to reduce the activation of endothelial NO synthase (eNOS), resulting in the reduction of NO [24]. The primary sources of ROS in the vasculature are nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, and uncoupled eNOS [25]. Particularly, NADPH oxidase has been found to be the most potent source of O_2^- in the human vasculature [26] and could be activated by LDL and high levels of free fatty acid [27, 28]. Thus, this would help explain the reduced endothelial function in obesity.

More specifically, obese individuals demonstrate elevated markers of ROS, including urinary 8-isoprostanes [2] and decreased antioxidant defenses, represented by lower antioxidant enzymes (e.g., SOD and catalase) [3]. Furthermore, in obese insulin-resistant individuals, the effect of insulin on eNOS is impaired and inducible NO synthase (iNOS) is stimulated, resulting in NO overproduction [29]. Evidence has demonstrated that when expressed iNOS is fully active, it can generate large amount of NO to react with O_2^- , resulting in elevated peroxynitrite ($ONOO^-$), a powerful reactive oxidant [30]. These findings are further supported by Perticone et al. [31] who demonstrated that abdominal fat distribution and insulin resistance are negatively correlated with forearm blood flow in response to acetylcholine infusion in obese individuals.

Although the mechanisms for obesity-induced oxidative stress remain unclear, leptin, an adipocyte-derived hormone, has been considered as an important contributor. Leptin is responsible for regulating energy intake and expenditure and is also known to play a key role in mediating pro-inflammatory state in obese individuals [8]. Korda et al. [7] have shown that elevated leptin induces oxidative stress (e.g., reduced NO and increased O_2^- and $ONOO^-$) in both human endothelial cells and the endothelium of obese mice. Yamagishi et al. [32] have further demonstrated that leptin can increase intracellular ROS generation in microvascular endothelial cells. Thus far, two possible mechanisms have been proposed for the leptin-induced oxidative stress: (i) the stimulation of mitochondrial oxidation of fatty acids [33] and (ii) the elevation of pro-inflammatory cytokines [34].

The pro-inflammatory state of the vessel can negatively impact oxidative stress and play a crucial role in the pathogenesis of obesity-related diseases. Elevated pro-inflammatory cytokines such as tumor necrosis factor (TNF- α) have been shown to downregulate the expression of eNOS (diminishing the dilatory response) in human aortic endothelial cells [34]. Specifically, TNF- α is a potent activator for activation of NADPH oxidase, resulting in the formation of ROS [35]. Picchi et al. [36] also examined the effects of TNF- α administration on oxidative stress response and found that higher O_2^- levels with reduced NO bioavailability in the coronary artery of Zucker obese rats compared to controls.

Interestingly, research has also shown that higher levels of leptin are associated with elevated pro-inflammatory cytokines (e.g., TNF- α and interleukin-6 [IL-6]) [37]. For example, *in vitro* a high dose of leptin has been found to elicit a great amount of TNF- α and IL-6 secretion from activated human peripheral blood mononuclear cells (PBMCs) [38]. In addition, macrophages play a vital role in regulating obese inflammation by the ability to shift T-helper (Th) cell differentiation toward the Th1 subtype, a pro-inflammatory condition [39]. Within the Th1 immune response, the most potent trigger for macrophage-induced ROS production is interferon-gamma (IFN- γ) [40]. Increased ROS such as O_2^- , H_2O_2 , and OH^- released by macrophages also provides a positive feedback to upregulate Th1 cell activation [41]. Importantly, leptin has been shown to serve as an immunological adjuvant to efficiently promote Th1 cell response [42]. Thus, inflammation and its subsequent impact on oxidative stress may play a crucial role in the pathogenesis of obesity-related diseases [43, 44].

Oxidative Stress and Physical Activity

Exercise-Induced Oxidative Stress

Exercise-induced oxidative stress has been shown to be dependent upon a number of factors including the mode [the form or type of exercise being utilized (cycling, jogging, and swimming)], intensity [percentage of maximal exercise capacity (VO_{2max})], and duration (total time exercising at a given percentage of VO_{2max}) of exercise being performed [45–49]. For example, concentrations of circulating oxidative stress markers were increasingly elevated at greater exercise intensities (25 vs. 50 vs. 75 % VO_{2peak}) following 30 min stationary cycling [45, 46] as well as at longer durations (120 vs. 60 vs. 30 min) following stationary cycling at 75 % VO_{2peak} [47]. Additionally, the characteristics of the participant (fitness or training levels, gender, and clinical disease status) can impact the resultant amount of oxidization that occurs [50, 51].

Research has shown that both acute aerobic [52–54] and anaerobic [55–57] exercise can result in increased

free radical production, propagating a potential increase in oxidative stress. Further, for oxidative stress to occur, the ROS and RNS produced during exercise must exceed the levels of the antioxidant available for cellular defense, thus resulting in oxidative damage to specific biomolecules [58]. As demonstrated in ironman competitors, the level of antioxidant defenses appear to be adequate to mitigate ROS/RNS production which occurs as a result of high-intensity, but shorter-duration exercise bouts (half ironman competitors), whereas in increasing intensity and/or duration of the acute bout (full ironman competitors), antioxidant defenses can no longer be maintained at sufficient levels, thereby resulting in oxidative damage to surrounding tissues [59]. Both single bouts of aerobic and anaerobic exercises (including resistance-type exercise) can induce oxidative stress, as indicated by the presence of oxidized molecules in a variety of tissue types, especially skeletal muscle [56, 57]. While acute bouts of exercise will lead to associated oxidative stress, these increases seem to be necessary in order to allow for an upregulation in endogenous antioxidant defenses, thus providing beneficial effects to the individual engaged in chronic exercise [60].

Interestingly, the mechanism for increased oxidative stress is somewhat different for aerobic and anaerobic activities. During aerobic exercise, mitochondrial respiration has been purported to produce ROS and RNS; whereas during anaerobic exercise and resistance training, it has been suggested that increases in free radical production may be tempered by enzymatic reactions, prostanoid metabolism, and/or altered calcium homeostasis [48, 49]. It has further been suggested that anaerobically induced oxidative stress may also result from the ischemia/reperfusion cycle of muscle contraction and/or immune system responses following muscle damage that occurs with anaerobic exercise [49, 55, 61]. Similar to aerobic exercise, the results of anaerobic investigations are currently unclear whether the observed increases in ROS and RNS represent a necessary stimulus for adaptation or a detrimental event. While the specific underlying factors that dictate the differences in responses between aerobic and anaerobic physical activities vary, the endpoint of both types of exercise is similar, an elevation in ROS and RNS [48, 62]. An elucidation of the distinct mechanisms may support proposals for different remediation strategies or interventions to limit oxidative stress.

Obesity-Related Oxidative Stress

Pro-inflammation has also shown to exert a negative oxidative effect in the skeletal muscle of obese individuals. Obese population exhibit decreased skeletal muscle strength and function compared to healthy weight subjects [63], as well as impaired skeletal muscle mitochondrial respiratory

function which contributes to increases in mitochondrial ROS production [64]. Specifically, obese individuals present higher ratios of type II to type I skeletal muscle fibers which have shown to generate two- to threefold more ROS production than type I fibers [64, 65]. Furthermore, Plomgaard et al. [66] demonstrated that TNF- α is solely expressed by type II muscle fibers and serves as a catalyst in skeletal muscle-derived oxidative stress [67]. Additionally, systemic TNF- α administration has been shown to diminish skeletal muscle force production in animal models [68] and directly promotes muscle protein loss [67] via oxidative activation of TNF- α /NF- κ B signaling [69]. Interestingly, TNF- α -induced skeletal muscle oxidative stress has been shown to be prevented by antioxidant treatment [67], suggesting that TNF- α may provide a vital target toward correcting obesity-related oxidative stress.

Of special interest is the fact that exercise-induced oxidative stress is exacerbated in obese populations, which has been shown in response to both acute aerobic and resistance exercises. Specifically, the total antioxidant status (TAS) in obese subjects decreased by 8.6 and 17.6 % in response to a single bout of aerobic and resistance exercises, respectively, whereas increases were observed in normal-weight individuals [50]. Furthermore, greater thiobarbituric reactive acid substances (TBARS), a marker of systemic oxidative stress, and lipid hydroperoxide (PEROX) increases were noted in obese subjects [50, 51]. Additionally, despite similar increases in PEROX levels in response to acute aerobic exercise in healthy obese and obese subjects with type 2 diabetes mellitus (T2DM), those with T2DM demonstrated greater decreases in TAS following exercise [70], suggesting a synergistic effect of metabolic dysfunction in further diminishing oxidative stress resistance. The authors suggested these outcomes may be the result of decreased availability of plasma vitamins C and E, elevated systolic blood pressure which may exacerbate vascular production of ROS during exercise, or greater mechanical and metabolic stress imposed by excessive adiposity; however, definitive reasoning remains yet to be elucidated. Finally, a number of assay techniques for the total antioxidant capacity have minimal sensitivity and specificity, thus the results for this measure have limited generalizability.

Physical Activity Intervention

Dietary CR as well as aerobic exercise, anaerobic exercise, and resistance training in association with weight loss has been shown to be advantageous in ameliorating oxidative stress and alleviating inflammation in obesity [71–77]. Specifically, overall oxidative stress, as indicated by TBARS and total PEROX, was reduced in healthy obese adults following 24 weeks of resistance-type circuit training [72], potentially due to increases in maximal oxygen consumption and fat-free mass and/or decreases in

total fat mass [73]. Additionally, Oh et al. [75] demonstrated that 12 weeks of moderate- to high-intensity aerobic training decreased TBARS and body weight in obese individuals, while baseline levels of the antioxidant GPX were increased following 6 months of aerobic training in obese women [78]. More importantly, following exercise intervention, acute exercise-induced increases in the oxidative stress marker malondialdehyde (MDA) were attenuated while SOD and GPX levels were increased compared to acute exercise-induced responses pre-training [78].

In the absence of weight loss, 3 months of aerobic training in previously sedentary healthy obese adults resulted in significant reductions in skeletal muscle-specific oxidative stress, as indicated by the urinary excretion marker 4-HNE and systemic 8-isoprostane and increased concentrations of mitochondrial antioxidants [79]. Utilizing a similar protocol, Derives et al. [80] reported similar alterations in systemic oxidative stress; however, no change in skeletal muscle 4-HNE expression was observed, suggesting that oxidative stress improvements also occur in other tissue sources. Furthermore, Youssef et al. [81] demonstrated that 12 weeks of moderate aerobic training in the absence of weight loss was also sufficient to attenuate exercise-induced increases of oxidized LDL (ox-LDL) and MPO following an acute bout of maximal aerobic exercise in overweight and obese adolescent girls compared to pre-training responses. Conversely, exercise without weight loss was not sufficient to improve any markers of oxidative stress in obese adolescents as result of 8-week exercise training, despite utilizing higher intensities of exercise [82]. In addition, none of the aforementioned protocols elicited improvements from a pro- to anti-inflammatory state in obese populations at baseline, suggesting that in obese populations: (i) exercise-induced improvements of systemic or skeletal muscle-specific oxidative stress may be the result of intensity and/or duration of the intervention, and (ii) weight loss may be necessary to alter inflammatory profiles.

Dietary Intervention

Although exercise training independent of weight loss beneficially increases antioxidant defenses and decreases oxidative stress at baseline and in response to exercise, previous studies suggest at least a 10 % reduction in body weight is necessary to reverse pro-inflammatory parameters which contribute to oxidative stress during obesity [71, 82, 83]. Dramatic weight loss (i.e., gastric bypass surgery) in previously obese men and women has been shown to decrease oxidative stress and vital inflammatory markers, such as IL-6, C-reactive protein, and TNF- α , suggesting that weight loss independently can reduce oxidative stress and inflammation [84, 85]. This strategy may not be feasible or advisable to the general

population; however, CR serves as an effective alternative. In animal models, 12 weeks of high-fat feeding increased NADPH oxidase, an important marker in the generation of oxidative stress, and accelerated the pathogenesis of endothelial dysfunction [86]. However, following high-fat diet, rodents underwent an additional 12 weeks of CR with and without exercise training, demonstrating a normalization of NADPH oxidase levels and reversal of the pathological progression of endothelial dysfunction. Furthermore, weight reductions of 10 % following 3 months of dietary restriction (500–1000 kcal/day energy deficit) in obese women resulted in increased glutathione reductase [87], while 6 months of hypocaloric diet elicited weight reductions of nearly 20 % which was sufficient to increase GPX and reduce 8-isoprostane, IL-6, and triglyceride levels in a manner associated with BMI reductions [88]. Additionally, alternate-day dietary restriction (20 %) resulted in a significant reduction in body weight and serum 4-HNE and 8-isoprostane while increasing antioxidant concentrations in obese adults [77]. TNF- α concentrations were also reduced after only 4 weeks, results which persisted throughout the 8-week study [77], potentially contributing to reduced production of cellular ROS [67]. Taken together, research suggests that significant weight fluctuations can directly dictate oxidative stress, inflammatory, and antioxidant enzyme profiles, processes which can be ameliorated through dietary weight loss intervention.

In obese individuals, 6 months of dieting coupled with aerobic exercise training designed to elicit a 10 % reduction in body weight also decreased overall oxidative stress [76]. Interestingly, Roberts et al. [89] reported decreases in oxidative stress accompanied with increases in TAS after only 3 weeks of combined strict dietary intervention and daily aerobic training. Despite no significant reductions in body weight, short-term diet and exercise intervention reduced *in vitro* expression of intracellular adhesion molecule (ICAM), a cellular adhesion marker which serves as an independent marker of CVD and vascular health. Furthermore, monocyte-derived monocyte chemoattractant protein-1 (MCP-1) production was attenuated, results which suggest that macrophage recruitment and exacerbation of the inflammatory response may be improved fairly quickly in response to lifestyle modifications in obese individuals.

Whether aerobic exercise may have a synergistic influence on long-term diet-induced improvements in oxidative stress and inflammatory profiles remains unclear. Wycherley et al. [74] demonstrated that while both diet and diet with aerobic exercise improved oxidative stress and NO availability and significantly reduced body weight, no difference between interventions was observed after 12 weeks in obese individuals with T2DM. Conversely, Ozcelik et al. [90] reported that hypocaloric diet coupled

with the weight loss supplement orlistat or aerobic exercise resulted in significant decreases in body weight; however, the diet plus exercise group exhibited significant decreases in oxidative stress while no difference was observed in the diet plus orlistat group.

Both aerobic and anaerobic activities possess the potential to result in increased ROS and RNS production and subsequent oxidative stress. While obesity has been shown to exacerbate the oxidative stress response, dietary manipulation and exercise training may serve as an effective intervention to ameliorate oxidative stress profiles. Whether exercise training improves oxidative stress and inflammatory profiles in the absence of weight loss remains unclear; however, strict CR alone or coupled with physical activity intervention demonstrates promise in alleviating oxidative stress in obese individuals when accompanied with weight reduction.

Macronutrient-Specific Postprandial Oxidative Stress

Increasing evidence suggests that *postprandial* metabolic responses along with biomarkers of oxidative stress may provide important information regarding an individual's susceptibility and/or progression of type 2 diabetes as well as other diseases [91, 92]. This is significant since the ingestion of calorie-rich meals may be associated with obesity [93]; however, the ingestion of energy-dense feedings may also elicit potentially deleterious metabolic responses that are independent of chronic weight gain. Several investigations have shown that both the amount [9] and composition [94–96] of macronutrient intake can affect postprandial oxidative stress responses. For example, the ingestion of moderate (75 g) and high (150 g) amounts of dextrose results in minimal oxidative stress as quantified by MDA and H_2O_2 [9]. However, the ingestion of 66 g of fat resulted in a significant increase of these two oxidative stress biomarkers [9], which was likely associated with postprandial superoxide production [97]. Varying results were reported following the ingestion of 33 g of fat [98], indicating that not only the source but also the amount of macronutrient distribution can have an effect on postprandial oxidative stress responses. Investigators have also been reported significant increases in postprandial triglycerides (TAG), MDA, H_2O_2 , and nitrate/nitrite following ingestion of a lipid meal compared to iso-caloric meals of varying macronutrient compositions [94]. Lipid-induced postprandial oxidative stress is likely explained by mitochondrial oxygen leakage and ROS generation [97, 99]. These results suggest potential “stress” associated with the ingestion of lipid-rich meals. It is important to note, however, that these responses can be affected by sex [100, 101]. Goldfarb and colleagues have suggested that this may be related to elevated glutathione status in women compared to men [102].

Interestingly, the magnitude of oxidative stress resulting from the ingestion of a lipid-rich meal has been shown to be greater than that resulting from strenuous exercise [103]. McCarthy et al. [103] was the first to investigate and compare oxidative stress responses from high-fat meals and acute bouts of strenuous exercise. Considering that the subjects in this study were exercise trained, it is possible that a training induced upregulated antioxidant defenses that contributed to the nonsignificant increase in oxidative stress in response to the strenuous exercise [103]. The potentially adverse effects associated with chronic ingestion of lipid-rich meals are apparent (weight gain) and may also be associated with additional ill health, including the development of insulin resistance [9]. Appropriate lifestyle modification (e.g., exercise and/or dietary interventions) seem to diminish oxidative stress and may positively influence diabetes [104] and vascular functioning [105].

Dietary Modifications and Oxidative Stress

Caloric restriction has been shown to be a successful weight loss intervention that may also improve markers of oxidative stress [106–109]. CR has been shown to promote longevity [110] as well as attenuate morbidity associated with several chronic diseases such as atherosclerosis, diabetes, cancer, autoimmune diseases, renal, neurodegenerative, and respiratory diseases [111]. This dietary modification has been shown to increase lifespan in rodents [112, 113]; however, these findings may not be universal among all animals. Further, a CR diet may be compared to an *ad libitum* diet which may contribute to excessive caloric intake and weight gain [114]. Hence, the validity for CR to promote longevity in humans currently remains a question due to a lack of longitudinal trials. Common approaches to CR include a relative change of macronutrient intake such as decreased carbohydrate or fat intake [115]. Both of which can be coupled with an increase in dietary protein intake. Of these approaches, a relative increase in dietary protein intake may actually contribute to decreased caloric intake since protein of various types (e.g., egg whites, dairy, lean meats) has been shown to have satiating properties [116]. In addition, although dietary fat is also known to induce satiety, higher fat intakes that are commonly coupled with low-carbohydrate diets [115] are potentially dangerous since this can serve as one source of postprandial oxidative stress [9, 94]. CR is usually practiced with a 20–40 % reduction of *ad libitum* dietary intake [117]. This approach has been shown to reduce biomarkers of oxidative stress such as H_2O_2 , protein carbonyls, and nitrotyrosine as well [106–109].

Two hypotheses have been proposed as potential mechanisms behind the benefits of CR [98]. The hormesis hypothesis suggests that CR acts as a low-intensity

stressor and thus, improvements in health and longevity can result as a defense against the exposure [118]. In addition, the oxidative damage hypothesis, which is supported in the literature, suggests that CR itself achieves the same goal by decreasing oxidative stress [119, 120]. Dietary fasting has been shown to prevent atherogenesis by improving NO bioavailability [121–123]. The Daniel Fast [98, 110, 124] is one type of dietary fast involving a plant-based feeding plan that restricts intake of animal products, refined foods, white flour, preservatives, additives, sweeteners, caffeine, and alcohol. Bloomer et al. [98] reported several benefits resulting from 21 days of this *ad libitum* dietary intervention. Improvements of oxidative stress biomarkers and antioxidant status were noted which included a significant reduction in MDA, an increase in nitrate/nitrite, and a 9 % increase in Trolox equivalent antioxidant capacity [98]. Also reported were improvements in blood lipids, glucose, insulin, systolic blood pressure, and body weight [98].

Another dietary modification that may increase antioxidant status, and thus protect against oxidative stress, is the increased consumption of selected micronutrients such as polyphenols [125, 126]. A wealth of data has supported the health benefits associated with increased fruit and vegetable consumption [127–130] which is likely related to the polyphenol antioxidant content [125, 126, 131]. Some classes of polyphenols include anthocyanins, lignans, flavonols, flavanones, flavanol monomers, proanthocyanidins, isoflavones, hydroxycinnamic acids, and hydroxybenzoic acids [126, 132]. Low consumption of fruits and vegetables and excessive fat intake serve as a major risk factor for an unfavorable imbalance between oxidants and antioxidants [9] and the development of chronic diseases contributing to morbidity and mortality [126].

Numerous studies have supported the link between the consumption of isolated antioxidants with benefits including improved antioxidant capacity [133], improved glucose metabolism [134], improved vascular function [135, 136], and attenuated LDL oxidation and progression of atherosclerosis [137]. Examples of these nutraceuticals that have been shown to improve various markers of oxidative stress include (but are not limited to) resveratrol [135, 136, 138, 139], α -lipoic acid [133, 140], ubiquinone (CoQ-10) [141], curcumin [134], quercetin [142], naringin [143], and lycopene [144]. Resveratrol and quercetin have been shown to activate sirtuin-1 (SIRT1) [145, 146]. Resveratrol is found in grapes and red wine [145] and is well known for its anticancer properties [147–149]. Several reports have investigated the SIRT1 activation activity of resveratrol and reported antioxidant, anti-inflammatory, antiapoptotic effects, as well as improvements in vascular functioning [135, 136]. Additional reports demonstrate that the deacetylase activity of SIRT1 is involved in proper glucose metabolism [150], indicating a potential implication

for the importance of SIRT1 and related antioxidants for the treatment of insulin resistance [151]. CR has also been shown to upregulate SIRT1 activity [151] as well as increase peroxisome proliferator activated receptor (PPAR)- γ coactivator-1 α (PGC-1 α) activity, which was associated with improved mitochondrial functioning as well as improvements in oxidative stress, insulin resistance, metabolic rate, and body composition [152]. These studies demonstrate the cellular adaptations that occur in response to CR that can impact oxidative stress.

The Potential of Vitamin D

Vitamin D insufficiency has shown to correlate with endothelial dysfunction [153], decreased cardiorespiratory fitness [154], and impaired skeletal muscle health, contributing to muscle weakness and decreased function [155]. Furthermore, these conditions may be reversed with vitamin D supplementation [156, 157]. Low vitamin D levels may also serve as a mechanism contributing to the exacerbation of oxidative stress during obesity, a condition worsened by elevated levels of TNF- α [69]; however, research remains limited. *In vivo*, the active vitamin D metabolite, 1,25(OH) $_2$ D $_3$, has been shown to downregulate ICAM-1 expression following peripheral blood mononuclear cell following exposure to TNF- α [158] while serving as an antioxidant at the cellular membrane by decreasing PEROX [159, 160] and increasing TAS as well as oxidative capacity in monocytes [161, 162]. Valcheva et al. [163] recently demonstrated that reactive oxygen species production is enhanced in mice deficient for the vitamin D receptor, while 12 weeks of supplementation decreases circulation markers of oxidative stress as well as improved lipid profiles in type 2 diabetics [164]. In addition, the risk of vitamin D insufficiency is elevated during obesity [165, 166], potentially due to increased sequestering of the steroid in adipose tissue [167]. In fact, for each 1 kg/m 2 increase in BMI, an estimated decrease of 0.74 nmol/L of vitamin D has been observed [168]. Importantly, vitamin D has been shown to inhibit the production of both TNF- α and IL-6 by downregulating the NF- κ B pathway [169, 170].

Tzotzas et al. [171] have provided evidence of the relationship of obesity to vitamin D. In their study, a 10 % reduction in weight resulted in increased vitamin D concentrations in previously vitamin D-insufficient obese individuals [171]. Furthermore, obese individuals supplemented with 3332 IU/day of vitamin D during weight loss intervention resulted in larger decreases in plasma TNF- α and IL-6 compared to placebo [172], while 1000 IU/day of vitamin D coupled with diet and exercise resulted in greater increases in VO $_{2max}$ and weight loss compared to either diet or exercise alone [173]. These results suggest a potential attenuation of oxidative stress in obese individuals supplemented with vitamin D, particularly

during exercise. Of note, there are no studies that have investigated the potential role of vitamin D supplementation to suppress oxidative stress in obese individuals during weight loss interventions.

Conclusions

Aerobic exercise, utilized to reduce obesity, results in an acute state of oxidative stress. However, it is likely that chronic physical activity provides a stimulus for favorable oxidative adaptations and enhanced physiological performance and physical health [13, 73]. Furthermore, while the specific underlying factors that dictate the differences in responses between aerobic and anaerobic exercises vary, the result for both is an elevation in biomarkers of oxidative stress [46, 62]. The mechanisms that would explain the potential benefits from chronic aerobic and anaerobic exercises have not been elucidated. Some have documented that a training-induced increase in endogenous antioxidant status may protect individuals against oxidative stress [78]. Without greater understanding of the distinct mechanisms, it is difficult to propose a specific activity that would result in a specific benefit or outcome.

Numerous studies support the benefits of dietary modification, including vitamin D supplementation, in alleviating oxidative stress; however, the interaction of obesity and physical activity has not been determined. Various metabolic, inflammatory, and cardiovascular mechanisms likely interact to explain the benefits of these interventions. Most importantly, further mechanistic investigations are necessary to determine the most effective intervention(s) for distinct benefits. It does seem evident that weight loss is significant in the alleviation of oxidative stress.

Oxidative stress is strongly associated with obesity, inflammation, vascular function, and diabetes [104, 105]. Appropriate lifestyle modifications can be taken (e.g., exercise training, dietary interventions) to alleviate oxidative stress. A greater understanding of the mechanisms associated with oxidative stress and disease can be utilized in the development of targeted treatment strategies to improve health.

Competing interest

C-JH, MM, ALS, HEW, JTM, and EOA declare that they have no competing interest, and no financial support was received for the conduct of this study or preparation of this manuscript.

Authors' contributions

All authors participated in the conception and design of the study and also read and approved the final manuscript.

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Received: 10 September 2015 Accepted: 11 September 2015

Published online: 23 September 2015

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