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Oxidative stress in obesity and insulin resistance

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Abstract

Since obesity is one of the main factors in the development of insulin resistance (IR) and is also associated with increased oxidative stress (OxS) rate, this study aims to review the published literature to collate and provide a comprehensive summary of the studies related to the status of the OxS in the pathogenesis of obesity and related IR. OxS represents an imbalance between the production of reactive oxygen and nitrogen species (RONS) and the capacity of the antioxidant defense system (AOS) to neutralize RONS. A steady-state of RONS level is maintained through endogenous enzymatic and non-enzymatic AOS components. Three crucial enzymes, which suppress the formation of free radicals, are superoxide dismutases, catalases, and glutathione peroxidases. The second line of AOS includes non-enzymatic components such as vitamins C and E, coenzyme Q, and glutathione which neutralizes free radicals by donating electrons to RONS. Emerging evidence suggests that high RONS levels contribute to the progression of OxS in obesity by activating inflammatory pathways and thus leading to the development of pathological states, including IR. In addition, decreased level of AOS components in obesity increases the susceptibility to oxidative tissue damage and further progression of its comorbidities. Increased OxS in accumulated adipose tissue should be an imperative target for developing new therapies in obesity-related IR.

Keywords

Antioxidant defense system, inflammation, insulin resistance, obesity, oxidative stress, reactive oxygen and nitrogen species

Introduction

Oxidative stress (OxS) derives from an imbalance between the production of reactive oxygen and nitrogen species (RONS) and the capacity of the antioxidant defense system (AOS) to neutralize RONS [1]. Primarily, RONS are crucial physiological modulators of the redox state signaling molecules and pathways. In OxS, RONS are directly or indirectly involved in oxidative degradation of nucleic acids, proteins, and lipids, leading to cell and tissue damages. The balanced level of RONS is maintained through a highly conserved

biochemical mechanism—AOS, which comprises endogenous enzymatic and non-enzymatic antioxidant components. The most important, first line of AOS, is comprised by the action of three vital enzymes: superoxide dismutases (SOD), catalases (CAT), and glutathione peroxidases (GPx) which prevent or suppress the formation of reactive species in cells. Non-enzymatic components of AOS include, among others, vitamins C and E, coenzyme Q, and glutathione (GSH), representing the second line of AOS, which neutralizes free radicals by donating electrons to RONS [2, 3]. Accumulating evidence suggests that RONS directly activate cellular pathways involved in the generation of OxS, leading to the progression of many different diseases, including carcinogenesis [4], neurodegeneration [5], acute brain ischemia [6], atherosclerosis [7, 8], and aging [9]. Furthermore, RONS-generating systems are involved in various pathophysiological processes such as inflammation, hypertension, and vascular remodeling, contributing to type 2 diabetes mellitus (T2DM), obesity, and hypercholesterolemia [10–15].

Obesity is a foremost underlying risk factor of several chronic diseases, including metabolic syndrome (MS), T2DM, cardiovascular diseases, fatty liver diseases, and cancer [16–24], all of which share a common pathological condition, insulin resistance (IR) [25]. Fat accumulation in the visceral tissues and organs in obesity leads to free fatty acids (FFAs) release into the portal circulation and further impairment of glucose metabolism. High glucose and lipids levels in circulation increase the energy substrates delivered to cellular metabolic pathways, increasing RONS production [26]. The association of elevated RONS production and generation of OxS in obesity is related to activation of the innate immune system in adipose tissue and subsequent low-grade chronic systemic inflammation [27]. Excessive adipose tissue is a source of pro-inflammatory cytokines that increase RONS production and lipid peroxidation rate [28], leading to OxS [27].

Numerous human and animal studies reported that the amount and activity of AOS components are decreased in obesity, increasing susceptibility to oxidative tissue damage [29–34]. Furthermore, an increase in RONS levels in adipose tissue of obese patients contributes to the generation of OxS and further progression to IR [25]. Additionally, factors that also contribute to OxS in obesity include hyperleptinemia [35], chronic inflammation [36], and postprandial ROS generation [37]. This review aims to explore, discuss, and summarize the latest literature data and current knowledge regarding the OxS in the pathogenesis of obesity and related IR.

AOS

A steady-state of RONS level is maintained through a complex AOS that includes endogenous enzymatic and non-enzymatic antioxidants. Non-enzymatic components of AOS are vitamins A, C, and E, polyphenols, alpha-lipoic acid, thioredoxin, GSH, melatonin, coenzyme Q, and β-carotenoids. Additionally, some proteins, such as ferritin, transferrin, lactoferrin, caeruloplasmin, act as antioxidants, binding and sequestering transition metals that may start oxidative reactions. The antioxidant enzymes include SOD, CAT, GPx, glutathione reductases (GR), glutathione-*S*-transferases, thioredoxin reductase, peroxiredoxins, and reduced nicotinamide adenine dinucleotide phosphate (NADPH):ubiquinone oxidoreductase [2, 3]. The components of AOS act at several different levels that may be radical preventive, radical scavenging, and radical-induced damage repair. The first line of defense antioxidants (SOD, CAT, and GPx) acts to prevent or suppress the formation of RONS in cells. The second line of defense antioxidants neutralizes free radicals by donating electrons, becoming free radicals of lesser damaging effects (vitamins C and E, coenzyme Q, and GSH) [2, 3]. There is also a third and fourth line of defense antioxidants based on defense lines. The DNA repair enzyme systems and proteolytic enzymes constitute the third line of defense antioxidants, which repair the damage caused by free radicals to biomolecules, and remove oxidized or damaged DNA [38], proteins, and lipids to prevent their toxic accumulation in the cell [39]. Fourth line defense antioxidants such as adaptation fundamentally implicate an adaptation mechanism in which the signal for the production and actions of free radicals induces formation and transport of the appropriate antioxidant to the right site [39].

Obesity and IR

A state of obesity is characterized by an increase in body mass and excessive fat accumulation in the visceral tissues and organs. Under continuous nutrient and energy exposure, the organism loses the ability to adapt and maintain homeostasis, and the consequent emergence of metabolic stress leads to inflammation and organelle dysfunction [40, 41]. As one of the leading endocrine organs in the body, adipose tissue is responsible for the production and secretion of multiple cytokines, chemokines, hormones, and other inflammatory mediators, collectively called adipokines [42]. Adipocytes represent the major cell type of adipose tissue and the primary source of adipokines, including adiponectin and leptin [43]. However, macrophages and T cells accumulate in adipose tissue of obese animals, leading to the increased expression of inflammatory marker molecules, including tumor necrosis factor-alpha (TNF-α) and inducible nitric oxide synthase [44]. Secreted adipokines act in a paracrine fashion, amplifying inflammation within the adipose tissue [45]. At the same time, adipokines pass into the circulation, promoting important systemic effects, which precedes a significant increase in circulating insulin levels [46]. The pancreatic β-cells synthesize and release supraphysiological insulin levels, keeping glucose metabolism equilibrated. Over time, IR arises, a pathological condition that implies the inability of peripheral tissues to sufficiently respond to insulin stimulation due to nutrient accumulation, OxS, and chronic inflammation. As the pancreas fails in overcoming IR with more insulin release, hyperglycemia and, eventually, diabetes develop [47].

OxS in obesity and IR

The production of RONS and generation of OxS associated with obesity are strongly related to the activation of the innate immune system in adipose tissue and subsequent low-grade chronic systemic inflammation [27]. Furthermore, during OxS, RONS are responsible for widespread lipid peroxidation in cells. Cell and tissue destruction mediated by radicals often enhance lipid peroxidation since the level of antioxidants is decreased, and transition metal ions, which stimulate the peroxidation process, are released from disrupted cells [27].

The presence of excessive adipose tissue has been identified as a source of pro-inflammatory cytokines TNF-α, interleukin-1 (IL-1), and IL-6, which generate an increase in RONS production and lipid peroxidation rate [28]. On the other hand, RONS induce the further release of pro-inflammatory cytokines and expression of adhesion molecules and growth factors [48] via activation of redox-sensitive transcription factors, such as nuclear factor kappa B (NFκB) and activator protein-1, and also the NADPH oxidase pathway (Figure 1) [49, 50].

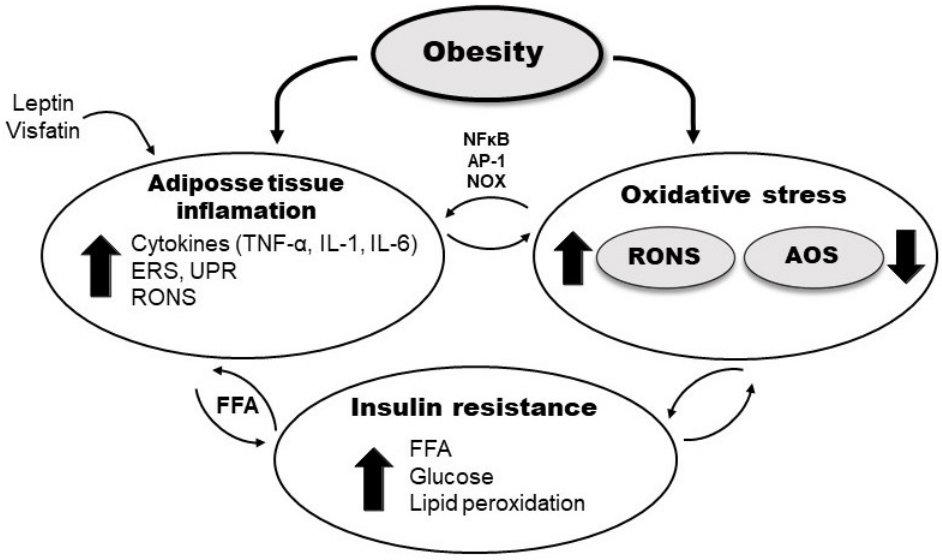

Figure 1. Schematic presentation of different pathways involved in OxS in obesity and IR. AP-1: activator protein-1, ERS: endoplasmic reticulum stress; NOX: NADPH oxidase; UPR: unfolded protein response

Additionally, OxS is associated with endoplasmic reticulum stress, during which misfolded proteins activate the UPR, responsible for protein folding and degradation of aberrantly packaged proteins. Prolonged UPR and oxidative protein folding machinery cause elevated RONS production followed by the systemic release of FFA and pro-inflammatory mediators [51]. Furthermore, some of the adipokines also induce the production of RONS, generating OxS and irregular production of other different adipokines [36]. The hormone leptin, secreted in adipocytes, exhibits pro-oxidative and pro-inflammatory effects, increasing macrophages' phagocytic activity, inducing the synthesis of pro-inflammatory cytokines, and increasing levels of endothelial cell dysfunction and activation markers [52]. In addition, visfatin is an adipokine that also shows pro-oxidant and pro-inflammatory effects, mediated by NFκB signaling pathway (Figure 1) [53].

An additional, important mechanism involved in generating OxS in obesity results from excessive accumulation of fat in the adipocytes, and this leads to a pathological increase of FFA in the serum, impairment of glucose metabolism, and accumulation of fat and glucose in the heart, liver, muscles, and pancreas [26]. As a result, mitochondrial and peroxisomal oxidation and the production of RONS increase, leading to OxS, mitochondrial DNA injury, depletion of ATP, and lipotoxicity [54, 55]. Moreover, a chronic increase in intracellular RONS levels in adipocytes due to mitochondrial dysfunction interferes with insulin signaling pathways and leads to the development of IR [56]. Also, high circulating glucose in obesity-induced IR could further enhance lipid peroxidation. Hyperglycemia may directly affect oxidative lipid and protein modification via the formation of glucose-derived free radicals in the protein glycation process [57]. Furthermore, β-cells of the pancreas exposed to hyperglycemia may produce RONS, suppressing insulin secretion induced by glucose [58]. Also, RONS themselves decrease the activity of the antioxidant enzymes, including CAT and GPx activity [59], and copper (Cu)/zinc (Zn)-SOD is reported to be inactivated by the glycation of specific lysine residue during hyperglycemia [60].

AOS in obesity and IR

β-cells of the pancreas have relatively low expression of many antioxidant enzymes, which makes β-cells susceptible to RONS-induced damage [61]. Glucotoxicity and lipotoxicity induce pancreatic β-cell dysfunction and liver IR, which are critical factors causing T2DM [62]. Accumulation of fat in the liver reduces the efficiency of antioxidant mechanisms in this organ, favoring OxS-related obesity [63]. Activities of SOD, CAT, and GPx are inversely related to body mass index (BMI) in obese children and adults [25, 64, 65]. AOS activity is also reduced in patients with MS [66, 67]. Furthermore, antioxidant defenses in obesity can also be impaired by deficiencies in minerals and non-enzymatic antioxidants [68].

Recently published data suggest that obesity is strictly linked to changes in redox state. Significant association of antioxidant defense parameters with anthropometric, lipid, and inflammatory markers has also been shown in obese young adults with increased risk of cardiovascular diseases [69, 70]. In addition, the latest advances in the field of obesity-related OxS biology are explorations regarding telomere length [71] and mitochondrial OxS [72, 73]. It shows that telomeres shorten according to the length of obesity phenotype and also to the degree of OxS influenced by obesity [71]. Furthermore, recent studies show the relevance of mitochondrial OxS in metabolic alterations associated with obesity and mitochondrial OxS in the dysbiosis associated with a high-fat diet (HFD) in rats [72, 73].

Evidence from animal studies

At the onset of obesity, antioxidant enzymes expression and activity increase in tissues to counteract the damaging effects of OxS which was reported in studies on animal models (Table 1). *In vitro* studies showed that extracellular (EC)-SOD expression is up-regulated in differentiated 3T3-L1 adipocytes of mice co-cultured with stimulated macrophages [74]. Thus, SOD may be stimulated to protect adipocytes from OxS generated by infiltrated macrophages [75]. In the heart of HFD-fed male mice, production of hydrogen peroxide (H_2O_2) increases and rapidly up-regulates CAT, probably to protect mitochondria from oxidative damage [76]. In the soleus muscle of the 4-week-old male Wistar rats fed on HFD for 14 days, a significantly lower total GSH level was observed, although there were no significant changes in the expression of GPx, CAT, and manganese (Mn)-SOD [77]. A fructose-enriched diet induces the development of IR in the white adipose tissue of the adult

female Wistar rats, although it did not lead to obesity and systemic IR. Thus, the protein levels of SOD1 and GR were increased in white adipose tissue of fructose-fed female rats, compared to the control group, which probably serve to prevent intracellular RONS accumulation and oxidative damage of macromolecules [78]. However, as obesity progresses, the amount and activity of the AOS components become depleted, increasing susceptibility to oxidative tissue damage [79]. The model of genetically obese (fa/fa) Zucker rats (ZR) share many features with human MS, such as obesity, IR, and hyperlipidemia [80]. In the study of Martinelli et al. [30], SOD activity was decreased in the plasma samples and the heart of obese male ZR compared to their lean littermates, while the activity of GPx was not significantly changed [30]. Additionally, the analysis showed an increase of oxidized proteins concentration and the expression of lipid-aldehyde 4-hydroxynonenal in the heart of obese male ZR. Increased pro-oxidative elements and the decreased components of AOS indicate a condition of obesity-related OxS in obese male ZR [30]. In male mice fed an HFD, the hepatic contents of GSH, GPx, and GR were significantly decreased [31], whereby serine supplementation increased the content of cysteine, one of the major determinants of GSH synthesis, thus protecting the liver against HFD-induced dysfunction of the GSH AOS. Krautbauer et al. [29] showed that the protein level of Mn-SOD is reduced in the liver of HFD-fed male mice [29]. In the visceral adipose tissue of young female Wistar rats, 9-week fructose-enriched diet led to a significant reduction of the protein levels of Mn-SOD and GPx, while protein levels of Cu/Zn-SOD and GR were unchanged [81]. Madani et al. [82] demonstrated that a fructose-rich diet led to a considerable increase of the plasma triglycerides and FFA levels, development of IR, and a substantial decrease of CAT, SOD, and GPx activities in adipose tissues in male Wistar rats. In male Albino rats, a high-fat and carbohydrate diet (HFCD) led to induction of IR, the increase of the malondialdehyde (MDA) level, and the decrease of GSH level. Moreover, the administration of the insulin-sensitizing drug pioglitazone to HFCD-induced IR rats reduced MDA level and improved GSH level, compared to the non-treated IR-induced group of rats [83].

Table 1. AOS in obesity and IR in animal model studies

Animal tissue/cell type	Components of AOS defense	Effect of obesity/IR	Ref
3T3-L1 adipocytes of mice	EC-SOD expression	Increased	[75]
Perirenal, epididymal, and brown adipose tissues of male Wistar rats	SOD, CAT, GPx activities	Decreased	[82]
Liver of male C57BL/6 mice	Mn-SOD protein level	Decreased	[29]
Heart of male C57BL/6J mice	CAT protein level/CAT activity	Increased	[76]
Visceral adipose tissue of female Wistar rats	Mn-SOD, GPx protein levels/Cu/Zn-SOD, GR protein levels	Decreased/unchanged	[81]
Primary hepatocytes of male C57BL/6J mice	GSH content, GPx, and GR activities	Decreased	[31]
Soleus muscle of Wistar male rats	Total GSH level/Mn-SOD, CAT, GPx expression	Decreased/unchanged	[77]
Plasma samples and heart of male fa/fa ZR	SOD/GPx activities	Decreased/unchanged	[30]
Serum of male Albino rats	MDA level/GSH level	Increased/decreased	[83]
White adipose tissue of female Wistar rats	SOD1 and GR protein levels	Increased	[78]

Ref: reference

Evidence from human studies

There is mounting evidence that attenuation of antioxidant enzymes and increased RONS production in obese subjects may contribute to further complications in obesity-related IR (Table 2). Irie et al. [33] found a significant decrease in serum GSH levels in male and female patients with non-alcoholic fatty liver disease, which can reduce the productivity of GSH-related antioxidant enzymes, such as GPx and GR. Depletion of GSH and reduced activities of GPx and GR have also been found in the serum of female T2DM patients [32]. A study showed that treating male and female T2DM patients with liraglutide led to an increase in serum GSH levels and a decrease of serum lipid hydroperoxides, thus reducing OxS in these patients [84]. In obese women, GPx activity significantly increases in the serum after mass body reduction [85]. In erythrocytes of obese women, Cu/Zn-SOD, GPx, and CAT activities were significantly lower compared to the same cell type of a normal-weight group [86]. In adipose tissue of obese male and female T2DM patients and non-diabetic obese

subjects and non-obese diabetic subjects, the mitochondrial Mn-SOD and GPx show decreased activities [87]. In peripheral blood mononuclear cells of obese children of both sexes, *Mn-SOD* and *CAT* gene expressions were significantly reduced compared to normal-weight children [34]. Obese children showed significantly higher levels of OxS markers MDA and 3-nitrotyrosine, and increased SOD activity compared with normal-weight children. Meanwhile, CAT concentration and the GSH/oxidized glutathione (GSSG) ratio correlated negatively with BMI. However, in children with overweight, SOD, CAT, and GSH/GSSG all correlated negatively with BMI [88]. In male and female patients with MS, the levels of oxidative markers, substances reactive to thiobarbituric acid and carbonyl protein, were increased, while the non-enzymatic antioxidants vitamin C and GSH were decreased [89]. Several experimental and clinical studies have shown a decrease in the serum paraoxonase (PON)-1 activity in obese subjects, which is positively correlated with BMI [90]. The PON family of antioxidant enzymes has an essential role in cardiovascular diseases and diabetes mellitus associated with obesity. PON-1 protects low-density lipoproteins and circulating cells against oxidative damage, preventing inflammatory responses in the arterial wall [91]. Selenium (Se) and Zn, which are important cofactors for GPx and SOD activities, are decreased in obese children and adolescents of both sexes [92, 93]. Magnesium (Mg), Se, Zn, and iron (Fe) have been reported deficiently in morbidly obese patients [94]. In the study by Aasheim and Bohmer [95], morbidly obese male and female patients have the most noticeable reduction in vitamins A, B6, C, D, and E. The cross-sectional study of Barzegar-Amini et al. [96] showed a significantly lower serum level of vitamin E in male and female patients with MS than patients without MS. Low carotenoids, vitamins C and E are related to increased BMI [97–99].

Table 2. AOS in obesity and IR in human studies

Human tissue/cell type	Components of AOS defense	Effect of obesity/IR	Ref
Serum of obese women	GPx activity	Decreased	[85]
Plasma of obese children of both sexes	Zn concentration	Decreased	[93]
Serum of morbidly obese male and female patients	Vitamins A, B6, C, D, E concentrations	Decreased	[95]
Serum of obese adolescents	Se concentration	Decreased	[92]
Erythrocytes of obese women	Cu/Zn-SOD, CAT, GPx activities	Decreased	[86]
Serum of male and female T2DM patients	GSH content/GPx, GR activities	Decreased	[32]
Adipose tissue of obese and/or T2DM male and female patients	Mn-SOD, GPx activities	Decreased	[87]
Serum and liver of male and female NAFLD patients	GSH level	Decreased	[33]
Peripheral blood mononuclear cells of obese children of both sexes	Mn-SOD, CAT expression	Decreased	[34]
Serum of MS male and female patients	Vitamin E concentration	Decreased	[96]
Blood samples of obese and overweight children	SOD activity/GSH/GSSG ratio, CAT activity	Increased/decreased (in obese); all decreased (in overweight)	[88]
Blood samples of MS male and female patients	Vitamin C, GSH levels	Decreased	[89]

NAFLD: non-alcoholic fatty liver disease

Conclusions

OxS has been implicated in the development of comorbidities in obesity and could be an early marker of metabolic dysfunction in obesity-related IR. Furthermore, obesity per se may induce systemic OxS, and increased OxS in accumulated adipose tissue is, at least in part, the underlying cause of adipocytokine dysregulation and MS development [100]. The excess supply of energy substrates to metabolic pathways in obesity may increase mitochondrial dysfunction and RONS production [101]. Notwithstanding, RONS are essential signaling molecules, if not well controlled, they can cause damage to cellular proteins, lipids, and DNA, potentially having detrimental effects on functions. While mounting evidence suggests that RONS overproduction in obesity leads to altered signaling and IR, other data reported that RONS is essential for insulin secretion by β-cells as well as insulin sensitivity [102, 103]. Increased OxS in accumulated adipose

tissue should be an imperative target for developing new therapies in obesity-related IR. A wide-ranging approach designed to decrease oxidation markers and improve antioxidant defenses in obese subjects includes weight loss associated with physical activity and different dietary factors, which could be helpful to prevent and treat obesity comorbidities.

Abbreviations

AOS: antioxidant defense system

BMI: body mass index

CAT: catalases

Cu: copper

FFAs: free fatty acids

GPx: glutathione peroxidases

GR: glutathione reductases

GSH: glutathione

GSSG: oxidized glutathione

HFD: high-fat diet

IL-1: interleukin-1

IR: insulin resistance

MDA: malondialdehyde

Mn: manganese

MS: metabolic syndrome

NADPH: reduced nicotinamide adenine dinucleotide phosphate

NFκB: nuclear factor kappa B

OxS: oxidative stress

PON: paraoxonase

RONS: reactive oxygen and nitrogen species

Se: selenium

SOD: superoxide dismutases

T2DM: type 2 diabetes mellitus

TNF-α: tumor necrosis factor-alpha

UPR: unfolded protein response

Zn: zinc

ZR: Zucker rats

Declarations

Author contributions

AP and JS wrote the manuscript and contributed conception. ERI and ESM designed, wrote, and supervised the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

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References

1. Takaki A, Kawai D, Yamamoto K. Multiple hits, including oxidative stress, as pathogenesis and treatment target in non-alcoholic steatohepatitis (NASH). Int J Mol Sci. 2013;14:20704–28.
2. Halliwell B, Rafter J, Jenner A. Health promotion by flavonoids, tocopherols, tocotrienols, and other phenols: direct or indirect effects? Antioxidant or not? Am J Clin Nutr. 2005;81:268S–76S.
3. Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. JAMA. 2014;311:33–44.
4. Trachootham D, Alexandre J, Huang P. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? Nat Rev Drug Discov. 2009;8:579–91.
5. Shukla V, Mishra SK, Pant HC. Oxidative stress in neurodegeneration. Adv Pharmacol Sci. 2011;2011:572634.
6. Radak D, Resanovic I, Isenovic ER. Link between oxidative stress and acute brain ischemia. Angiology. 2014;65:667–76.
7. Paravicini TM, Touyz RM. Redox signaling in hypertension. Cardiovasc Res. 2006;71:247–58.
8. Obradovic M, Bogdanovic N, Radak D, Isenovic ER. Editorial: oxidative stress in pathophysiological conditions. Curr Vasc Pharmacol. 2015;13:226–8.
9. Haigis MC, Yankner BA. The aging stress response. Mol Cell. 2010;40:333–44.
10. Al Ghouleh I, Khoo NKH, Knaus UG, Griendling KK, Touyz RM, Thannickal VJ, et al. Oxidases and peroxidases in cardiovascular and lung disease: new concepts in reactive oxygen species signaling. Free Radic Biol Med. 2011;51:1271–88.
11. Bir SC, Kolluru GK, Fang K, Kevil CG. Redox balance dynamically regulates vascular growth and remodeling. Semin Cell Dev Biol. 2012;23:745–57.
12. Tabet F, Schiffrin EL, Callera GE, He Y, Yao G, Ostman A, et al. Redox-sensitive signaling by angiotensin II involves oxidative inactivation and blunted phosphorylation of protein tyrosine phosphatase SHP-2 in vascular smooth muscle cells from SHR. Circ Res. 2008;103:149–58.
13. Togliatto G, Lombardo G, Brizzi MF. The future challenge of reactive oxygen species (ROS) in hypertension: from bench to bed side. Int J Mol Sci. 2017;18:1988.
14. Haidara MA, Yassin HZ, Zakula Z, Mikhailidis DP, Isenovic ER. Diabetes and antioxidants: myth or reality? Curr Vasc Pharmacol. 2010;8:661–72.

15. Obradovic M, Essack M, Zafirovic S, Sudar-Milovanovic E, Bajic VP, Van Neste C, et al. Redox control of vascular biology. Biofactors. 2020;46:246–62.
16. Sikaris KA. The clinical biochemistry of obesity. Clin Biochem Rev. 2004;25:165–81.
17. Sudar EM, Zafirovic SS, Dobutovic BD, Obradovic MM, Soskic S, Jovanovic AA, et al. Obesity as a risk factor for cardiovascular diseases: one of the biggest problems in health care today. Life Safety and Security. 2013;1:5–17.
18. Sudar Milovanovic E, Jovanovic A, Misirkic-Marjanovic M, Vucicevic L, Janjetovic K, Isenovic ER. Effects of intracerebroventricularly (ICV) injected ghrelin on cardiac inducible nitric oxide synthase activity/expression in obese rats. Exp Clin Endocrinol Diabetes. 2015;123:581–8.
19. Jovanovic A, Sudar-Milovanovic E, Obradovic M, Pitt SJ, Stewart AJ, Zafirovic S, et al. Influence of a high-fat diet on cardiac iNOS in female rats. Curr Vasc Pharmacol. 2017;15:491–500.
20. Panic A, Stanimirovic J, Obradovic M, Sudar-Milovanovic E, Perovic M, Lackovic M, et al. Estradiol-mediated regulation of hepatic iNOS in obese rats: impact of Src, ERK1/2, AMPKalpha, and miR-221. Biotechnol Appl Biochem. 2018;65:797–806.
21. Stanimirovic J, Obradovic M, Jovanovic A, Sudar-Milovanovic E, Zafirovic S, Pitt SJ, et al. A high fat diet induces sex-specific differences in hepatic lipid metabolism and nitrite/nitrate in rats. Nitric Oxide. 2016;54:51–9.
22. Essack M, Salhi A, Stanimirovic J, Tifratene F, Bin Raies A, Hungler A, et al. Literature-based enrichment insights into redox control of vascular biology. Oxid Med Cell Longev. 2019;2019:1769437.
23. Vucic V, Isenovic ER, Adzic M, Ruzdijic S, Radojcic MB. Effects of gamma-radiation on cell growth, cycle arrest, death, and superoxide dismutase expression by DU 145 human prostate cancer cells. Braz J Med Biol Res. 2006;39:227–36.
24. Bajic VP, Van Neste C, Obradovic M, Zafirovic S, Radak D, Bajic VB, et al. Glutathione "dox homeostasis" and its relation to cardiovascular disease. Oxid Med Cell Longev. 2019;2019:5028181.
25. Olivares-Corichi IM, Viquez MJ, Gutierrez-Lopez L, Ceballos-Reyes GM, Garcia-Sanchez JR. Oxidative stress present in the blood from obese patients modifies the structure and function of insulin. Horm Metab Res. 2011;43:748–53.
26. Tereshin EV. A role of fatty acids in the development of oxidative stress in aging. A hypothesis. Adv Gerontol. 2007;20:59–65. Russian.
27. Hensley K, Robinson KA, Gabbita SP, Salsman S, Floyd RA. Reactive oxygen species, cell signaling, and cell injury. Free Radic Biol Med. 2000;28:1456–62.
28. Khan NI, Naz L, Yasmeen G. Obesity: an independent risk factor for systemic oxidative stress. Pak J Pharm Sci. 2006;19:62–5.
29. Krautbauer S, Eisinger K, Lupke M, Wanninger J, Ruemmele P, Hader Y, et al. Manganese superoxide dismutase is reduced in the liver of male but not female humans and rodents with non-alcoholic fatty liver disease. Exp Mol Pathol. 2013;95:330–5.
30. Martinelli I, Tomassoni D, Moruzzi M, Roy P, Cifani C, Amenta F, et al. Cardiovascular changes related to metabolic syndrome: evidence in obese Zucker rats. Int J Mol Sci. 2020;21:2035.
31. Zhou X, He L, Zuo S, Zhang Y, Wan D, Long C, et al. Serine prevented high-fat diet-induced oxidative stress by activating AMPK and epigenetically modulating the expression of glutathione synthesis-related genes. Biochim Biophys Acta Mol Basis Dis. 2018;1864:488–98.
32. Aouacheri O, Saka S, Krim M, Messaadia A, Maidi I. The investigation of the oxidative stress-related parameters in type 2 diabetes mellitus. Can J Diabetes. 2015;39:44–9.
33. Irie M, Sohda T, Anan A, Fukunaga A, Takata K, Tanaka T, et al. Reduced glutathione suppresses oxidative stress in nonalcoholic fatty liver disease. Euroasian J Hepatogastroenterol. 2016;6:13–8.

34. Mohseni R, Arab Sadeghabadi Z, Goodarzi MT, Teimouri M, Nourbakhsh M, Razzaghy Azar M. Evaluation of Mn-superoxide dismutase and catalase gene expression in childhood obesity: its association with insulin resistance. J Pediatr Endocrinol Metab. 2018;31:727–32.
35. Bełtowski J. Leptin and the regulation of endothelial function in physiological and pathological conditions. Clin Exp Pharmacol Physiol. 2012;39:168–78.
36. Fernandez-Sanchez A, Madrigal-Santillan E, Bautista M, Esquivel-Soto J, Morales-Gonzalez A, Esquivel-Chirino C, et al. Inflammation, oxidative stress, and obesity. Int J Mol Sci. 2011;12:3117–32.
37. Patel C, Ghanim H, Ravishankar S, Sia CL, Viswanathan P, Mohanty P, et al. Prolonged reactive oxygen species generation and nuclear factor-kappaB activation after a high-fat, high-carbohydrate meal in the obese. J Clin Endocrinol Metab. 2007;92:4476–9.
38. Bajic V, Spremo-Potparevic B, Zivkovic L, Cabarkapa A, Kotur-Stevuljevic J, Isenovic E, et al. Surface-modified TiO_2 nanoparticles with ascorbic acid: antioxidant properties and efficiency against DNA damage *in vitro*. Colloids Surf B Biointerfaces. 2017;155:323–31.
39. Ighodaro OM, Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): their fundamental role in the entire antioxidant defence grid. Alexandria Journal of Medicine. 2018;54:287–93.
40. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444:860–7.
41. Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell. 2010;140:900–17.
42. Rocha VZ, Libby P. The multiple facets of the fat tissue. Thyroid. 2008;18:175–83.
43. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S, Stewart AJ, et al. Leptin and obesity: role and clinical implication. Front Endocrinol (Lausanne). 2021;12:585887.
44. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest. 2007;117:175–84.
45. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006;116:1793–801.
46. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol. 2011;29:415–45.
47. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005;365:1333–46.
48. Lavrovsky Y, Chatterjee B, Clark RA, Roy AK. Role of redox-regulated transcription factors in inflammation, aging and age-related diseases. Exp Gerontol. 2000;35:521–32.
49. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. Gastroenterology. 2007;132:2169–80.
50. Bryan S, Baregzay B, Spicer D, Singal PK, Khaper N. Redox-inflammatory synergy in the metabolic syndrome. Can J Physiol Pharmacol. 2013;91:22–30.
51. Wang S, Kaufman RJ. The impact of the unfolded protein response on human disease. J Cell Biol. 2012;197:857–67.
52. Hukshorn CJ, Lindeman JHN, Toet KH, Saris WHM, Eilers PHC, Westerterp-Plantenga MS, et al. Leptin and the proinflammatory state associated with human obesity. J Clin Endocrinol Metab. 2004;89:1773–8.
53. Kim SR, Bae YH, Bae SK, Choi KS, Yoon KH, Koo TH, et al. Visfatin enhances ICAM-1 and VCAM-1 expression through ROS-dependent NF-kappaB activation in endothelial cells. Biochim Biophys Acta. 2008;1783:886–95.
54. Rzheshevsky AV. Fatal "triad": lipotoxicity, oxidative stress, and phenoptosis. Biochemistry (Mosc). 2013;78:991–1000.
55. Goossens GH. The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. Physiol Behav. 2008;94:206–18.

56. Wang CH, Wang CC, Huang HC, Wei YH. Mitochondrial dysfunction leads to impairment of insulin sensitivity and adiponectin secretion in adipocytes. FEBS J. 2013;280:1039–50.
57. Wolff SP, Jiang ZY, Hunt JV. Protein glycation and oxidative stress in diabetes mellitus and ageing. Free Radic Biol Med. 1991;10:339–52.
58. Sakai K, Matsumoto K, Nishikawa T, Suefuji M, Nakamaru K, Hirashima Y, et al. Mitochondrial reactive oxygen species reduce insulin secretion by pancreatic beta-cells. Biochem Biophys Res Commun. 2003;300:216–22.
59. Datta K, Sinha S, Chattopadhyay P. Reactive oxygen species in health and disease. Natl Med J India. 2000;13:304–10.
60. Oda A, Bannai C, Yamaoka T, Katori T, Matsushima T, Yamashita K. Inactivation of Cu,Zn-superoxide dismutase by *in vitro* glycosylation and in erythrocytes of diabetic patients. Horm Metab Res. 1994;26:1–4.
61. Pi J, Bai Y, Zhang Q, Wong V, Floering LM, Daniel K, et al. Reactive oxygen species as a signal in glucose-stimulated insulin secretion. Diabetes. 2007;56:1783–91.
62. Yang J, Kang J, Guan Y. The mechanisms linking adiposopathy to type 2 diabetes. Front Med. 2013;7:433–44.
63. Basaranoglu M, Kayacetin S, Yilmaz N, Kayacetin E, Tarcin O, Sonsuz A. Understanding mechanisms of the pathogenesis of nonalcoholic fatty liver disease. World J Gastroenterol. 2010;16:2223–6.
64. Viroonudomphol D, Pongpaew P, Tungtrongchitr R, Phonrat B, Supawan V, Vudhivai N, et al. Erythrocyte antioxidant enzymes and blood pressure in relation to overweight and obese Thai in Bangkok. Southeast Asian J Trop Med Public Health. 2000;31:325–34.
65. Mittal PC, Kant R. Correlation of increased oxidative stress to body weight in disease-free post menopausal women. Clin Biochem. 2009;42:1007–11.
66. Hopps E, Noto D, Caimi G, Averna MR. A novel component of the metabolic syndrome: the oxidative stress. Nutr Metab Cardiovasc Dis. 2010;20:72–7.
67. Haidara M, Mikhailidis DP, Yassin HZ, Dobutovic B, Smiljanic KT, Soskic S, et al. Evaluation of the possible contribution of antioxidants administration in metabolic syndrome. Curr Pharm Des. 2011;17:3699–712.
68. Via M. The malnutrition of obesity: micronutrient deficiencies that promote diabetes. ISRN Endocrinol. 2012;2012:103472.
69. Colak E, Pap D, Nikolic L, Vickovic S. The impact of obesity to antioxidant defense parameters in adolescents with increased cardiovascular risk. J Med Biochem. 2020;39:346–54.
70. Jakubiak GK, Osadnik K, Lejawa M, Kasperczyk S, Osadnik T, Pawlas N. Oxidative stress in association with metabolic health and obesity in young adults. Oxid Med Cell Longev. 2021;2021:9987352.
71. Lejawa M, Osadnik K, Osadnik T, Pawlas N. Association of metabolically healthy and unhealthy obesity phenotypes with oxidative stress parameters and telomere length in healthy young adult men. Analysis of the magnetic study. Antioxidants (Basel). 2021;10:93.
72. Souza-Neto FV, Jimenez-Gonzalez S, Delgado-Valero B, Jurado-Lopez R, Genty M, Romero-Miranda A, et al. The interplay of mitochondrial oxidative stress and endoplasmic reticulum stress in cardiovascular fibrosis in obese rats. Antioxidants (Basel). 2021;10:1274.
73. Ortega-Hernandez A, Martinez-Martinez E, Gomez-Gordo R, Lopez-Andres N, Fernandez-Celis A, Gutierrrez-Miranda B, et al. The interaction between mitochondrial oxidative stress and gut microbiota in the cardiometabolic consequences in diet-induced obese rats. Antioxidants (Basel). 2020;9:640.
74. Adachi T, Toishi T, Takashima E, Hara H. Infliximab neutralizes the suppressive effect of TNF-alpha on expression of extracellular-superoxide dismutase *in vitro*. Biol Pharm Bull. 2006;29:2095–8.

75. Adachi T, Toishi T, Wu H, Kamiya T, Hara H. Expression of extracellular superoxide dismutase during adipose differentiation in 3T3-L1 cells. Redox Rep. 2009;14:34–40.

76. Rindler PM, Plafker SM, Szweda LI, Kinter M. High dietary fat selectively increases catalase expression within cardiac mitochondria. J Biol Chem. 2013;288:1979–90.

77. Andrich DE, Melbouci L, Ou Y, Auclair N, Mercier J, Grenier JC, et al. A short-term high-fat diet alters glutathione levels and *IL-6* gene expression in oxidative skeletal muscles of young rats. Front Physiol. 2019;10:372.

78. Kovacevic S, Brkljacic J, Vojnovic Milutinovic D, Gligorovska L, Bursac B, Elakovic I, et al. Fructose induces visceral adipose tissue inflammation and insulin resistance even without development of obesity in adult female but not in male rats. Front Nutr. 2021;8:749328.

79. Horvath TL, Andrews ZB, Diano S. Fuel utilization by hypothalamic neurons: roles for ROS. Trends Endocrinol Metab. 2009;20:78–87.

80. Tomassoni D, Nwankwo IE, Gabrielli MG, Bhatt S, Muhammad AB, Lokhandwala MF, et al. Astrogliosis in the brain of obese Zucker rat: a model of metabolic syndrome. Neurosci Lett. 2013;543:136–41.

81. Kovacevic S, Nestorov J, Matic G, Elakovic I. Fructose-enriched diet induces inflammation and reduces antioxidative defense in visceral adipose tissue of young female rats. Eur J Nutr. 2017;56:151–60.

82. Madani Z, Louchami K, Sener A, Malaisse WJ, Ait Yahia D. Dietary sardine protein lowers insulin resistance, leptin and TNF-alpha and beneficially affects adipose tissue oxidative stress in rats with fructose-induced metabolic syndrome. Int J Mol Med. 2012;29:311–8.

83. Al-Muzafar HM, Alshehri FS, Amin KA. The role of pioglitazone in antioxidant, anti-inflammatory, and insulin sensitivity in a high fat-carbohydrate diet-induced rat model of insulin resistance. Braz J Med Biol Res. 2021;54:e10782.

84. Rizzo M, Abate N, Chandalia M, Rizvi AA, Giglio RV, Nikolic D, et al. Liraglutide reduces oxidative stress and restores heme oxygenase-1 and ghrelin levels in patients with type 2 diabetes: a prospective pilot study. J Clin Endocrinol Metab. 2015;100:603–6.

85. Bougoulia M, Triantos A, Koliakos G. Plasma interleukin-6 levels, glutathione peroxidase and isoprostane in obese women before and after weight loss. Association with cardiovascular risk factors. Hormones (Athens). 2006;5:192–9.

86. Amirkhizi F, Siassi F, Djalali M, Shahraki SH. Impaired enzymatic antioxidant defense in erythrocytes of women with general and abdominal obesity. Obes Res Clin Pract. 2014;8:e26–34.

87. Chattopadhyay M, Khemka VK, Chatterjee G, Ganguly A, Mukhopadhyay S, Chakrabarti S. Enhanced ROS production and oxidative damage in subcutaneous white adipose tissue mitochondria in obese and type 2 diabetes subjects. Mol Cell Biochem. 2015;399:95–103.

88. Fuentes-Venado CE, Teran-Perez G, Espinosa-Hernandez VM, Martinez-Herrera E, Segura-Uribe JJ, Mercadillo RE, et al. Nutritional status influences oxidative stress and insulin resistance in preschool children. Metab Syndr Relat Disord. 2021;19:513–23.

89. Martins CC, Bagatini MD, Simoes JLB, Cardoso AM, Baldissarelli J, Dalenogare DP, et al. Increased oxidative stress and inflammatory markers contrasting with the activation of the cholinergic anti-inflammatory pathway in patients with metabolic syndrome. Clin Biochem. 2021;89:63–9.

90. D'rchivio M, Annuzzi G, Vari R, Filesi C, Giacco R, Scazzocchio B, et al. Predominant role of obesity/insulin resistance in oxidative stress development. Eur J Clin Invest. 2012;42:70–8.

91. Savini I, Catani MV, Evangelista D, Gasperi V, Avigliano L. Obesity-associated oxidative stress: strategies finalized to improve redox state. Int J Mol Sci. 2013;14:10497–538.

92. Ortega RM, Rodriguez-Rodriguez E, Aparicio A, Jimenez-Ortega AI, Palmeros C, Perea JM, et al. Young children with excess of weight show an impaired selenium status. Int J Vitam Nutr Res. 2012;82:121–9.

93. Weisstaub G, Hertrampf E, Lopez de Romana D, Salazar G, Bugueno C, Castillo-Duran C. Plasma zinc concentration, body composition and physical activity in obese preschool children. Biol Trace Elem Res. 2007;118:167–74.
94. Kaidar-Person O, Person B, Szomstein S, Rosenthal RJ. Nutritional deficiencies in morbidly obese patients: a new form of malnutrition? Part B: minerals. Obes Surg. 2008;18:1028–34.
95. Aasheim ET, Bohmer T. Low preoperative vitamin levels in morbidly obese patients: a role of systemic inflammation? Surg Obes Relat Dis. 2008;4:779–80.
96. Barzegar-Amini M, Khorramruz F, Ghazizadeh H, Sahebi R, Mohammadi-Bajgyran M, Mohaddes Ardabili H, et al. Association between serum vitamin E concentrations and the presence of metabolic syndrome: a population-based cohort study. Acta Biomed. 2021;92:e2021047.
97. Kaidar-Person O, Person B, Szomstein S, Rosenthal RJ. Nutritional deficiencies in morbidly obese patients: a new form of malnutrition? Part A: vitamins. Obes Surg. 2008;18:870–6.
98. Schleicher RL, Carroll MD, Ford ES, Lacher DA. Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003–2004 National Health and Nutrition Examination Survey (NHANES). Am J Clin Nutr. 2009;90:1252–63.
99. Reitman A, Friedrich I, Ben-Amotz A, Levy Y. Low plasma antioxidants and normal plasma B vitamins and homocysteine in patients with severe obesity. Isr Med Assoc J. 2002;4:590–3.
100. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest. 2004;114:1752–61.
101. Bournat JC, Brown CW. Mitochondrial dysfunction in obesity. Curr Opin Endocrinol Diabetes Obes. 2010;17:446–52.
102. Leloup C, Tourrel-Cuzin C, Magnan C, Karaca M, Castel J, Carneiro L, et al. Mitochondrial reactive oxygen species are obligatory signals for glucose-induced insulin secretion. Diabetes. 2009;58:673–81.
103. Loh K, Deng H, Fukushima A, Cai X, Boivin B, Galic S, et al. Reactive oxygen species enhance insulin sensitivity. Cell Metab. 2009;10:260–72.