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Oxidative stress and obesity

Maja Malenica[1]*, Neven Meseldžić[1]

[1]University of Sarajevo - Faculty of Pharmacy, Department of Pharmaceutical Biochemistry and Laboratory Diagnostics, Zmaja od Bosne 8, 71000 Sarajevo, Bosnia and Herzegovina

*Corresponding author: Maja Malenica, e-mail: maja.malenica@ffsa.unsa.ba

Abstract

Obesity is a disease of excessive accumulation of adipose tissue due to an increased energy intake which is disproportionate to the energy expenditure in the body. The visceral adipose tissue in the obese accumulated in that way increases the risk of developing a number of metabolic and cardiovascular diseases. Disorders such as diabetes, dyslipidemia, inflammation, endothelial dysfunction and mitochondria can contribute to the development of oxidative stress, which is especially pronounced in the abdominal type of obesity. Obesity can induce systemic oxidative stress through a variety of biochemical mechanisms. Although ROS is generated in a large number of cells, mitochondria play a significant role in their intracellular production through the process of oxidative phosphorylation of the respiratory chain, and in fatty acid oxidation reactions. Oxidative stress is a unique link between the various molecular disorders present in the development of insulin resistance that plays a key role in the pathogenesis and progression of chronic metabolic, proinflammatory diseases. The progression of insulin resistance is also affected by inflammation. Both of these can be the cause and the consequence of obesity. The synthesis of the inflammatory mediators is induced by oxidative stress, thus bringing the inflammation and the oxidative stress into a very significant relation. This review aims to highlight recent findings on the role of oxidative stress in the pathogenesis of obesity, with special reference to the mechanisms that explain its occurrence.

Key words: oxidative stress, insulin resistance, inflammation, biomarkers

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Introduction

Obesity is one of the most common modern diseases, and has reached pandemic proportions in recent years. The prevalence of obesity in the world is constantly increasing and in the last few years more than 2 billion adults (39% of the world's adult population) have been overweight (BMI> 25) and 13% have been obese (BMI> 30) (1). In Europe, more than half of the population is overweight, and up to 30% are obese (2,3). One of the most at-risk groups in terms of malnutrition and obesity is that of children and adolescents (4). The social impact and "civilization benefits" of modern society also contribute to increasing the prevalence of obesity, which is one of the most significant health problems of today. Obesity happens as a result of excessive energy intake through food, and insufficient energy consumption as a consequence of a sedentary lifestyle. We can define it as a disease caused by excess body fat, and it is often accompanied by other pathological conditions of the body, the most common of which are type 2 diabetes (T2D), insulin resistance (IR), cardiovascular diseases, including hypertension and atherosclerosis, dyslipidemia, chronic kidney disease and tumors. In addition to the above, many diseases appear to a lesser extent.

Nowadays, the pronounced metabolic activity of the adipose tissue is very well-known because it secretes numerous adipo/cytokines, which have proinflammatory, proatherogenic and prothrombotic effects, so fat accumulation is associated with pro-oxidative and pro-inflammatory conditions. Such conditions contribute to a number of disorders of glucose metabolism, lipids and/or markers of inflammation, which is considered a trigger for oxidative stress. This comprehensively leads to the development of a number of complex diseases (hypertension, coronary heart disease, T2D, metabolic syndrome) which directly affect the quality of life (5). Numerous studies show a reversible relationship between obesity and oxidative stress where a cause-and-effect relationship between the two conditions is still being established. Biochemical processes affected by oxidative stress due to increased adiposity are glyceraldehyde autooxidation, oxidative phosphorylation, protein kinase C activation, increased production of superoxide radicals by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and metabolic pathways of hexosamine and polyol (6). On the other hand, oxidative stress is considered to be a key factor in the development of obesity because it stimulates the deposition of adipose tissue. It is possible to see and interpret the mechanisms that link obesity and metabolic disorders caused by it from several perspectives. Therefore, the network of these mechanisms is very intertwined and still insufficiently clarified. It is a well-known fact that in the state of obesity, due to an increased amount of adipose tissue, inflammation, oxidative stress and insulin resistance are activated due to an abnormal inflammatory response, reduced antioxidants and reduced insulin sensitivity (7). In addition to stimulating the inflammatory response, adipose tissue expansion also results in an increased production of reactive oxygen species (ROS).

The formation of free radicals can be considered as a continuous physiological process that satisfies the relevant biological functions. Namely, reactive oxygen radicals and reactive nitrogen species (RNS) are formed as products in metabolism. Although their

concentrations in the cell are very low and have a short half-life, free radicals are very reactive (8). During metabolic processes, these radicals act as mediators in electron transfer as a part of various biochemical reactions that take place at the level of mitochondria, cell membranes and cytoplasm. Namely, they have a dual role in biological systems. The first one is the physiological role, which implies their participation in the defense against infectious agents and in a number of cellular signaling systems, followed by the induction of mitosis at low concentrations. In contrast, at high concentrations, ROS are important mediators of damage at the level of cellular structures that include lipids, proteins, and nucleic acids. The issue with the normal functioning of the organism arises when the "fine" homeostasis of oxido-reduction processes moves in the direction of oxidation. In that case, the level of free radicals exceeds the capacity of the organism to neutralize them, the oxidative status changes and the body enters the zone of increased oxidative stress, i.e., a state of increased risk of many metabolic disorders. The hyperproduction of adipose tissue leads to an imbalance in the energy homeostasis, which results in the infiltration of inflammatory cells into adipose tissue and its expansion (9,10). Inflammatory molecules created in both adipocytes and macrophages are part of a complex process of developing IR and systemic inflammation that together cause the formation of ROS. As a provocative response, ROS leads to adipose tissue inflammation, and thus to IR and inflammation in general (11).

Relationship between oxidative stress, insulin resistance and inflammation in obesity

Oxidative stress through ROS production represents a unique link between the various molecular disorders present in the IR development, beta cell dysfunction, and glucose tolerance disorders (12). IR plays a key role in the pathogenesis and progression of chronic metabolic, by their nature, proinflammatory diseases, because it appears as a phenomenon before the onset of metabolic complications. Oxidative stress and inflammation are key factors in the progression of IR in general, which favors the occurrence of obesity and T2D, and thus a large number of comorbidities. Therefore, inflammation is one of the manifestations of oxidative stress because the pathways in which inflammatory mediators are formed, such as adhesion molecules or interleukins, are induced by oxidative stress. Mechanisms explaining how oxidative stress contributes to the development of the IR state, in the case of obesity-T2D, include the regulation of the pentose phosphate cycle (13). Namely, in experimental rats where a fat-rich diet was induced, high levels of oxidative stress accompanied by IR occurred. Glycogen synthesis was increased, but glycolysis was inhibited (decrease in phosphofructokinase (PFK), pyruvate kinase (PK), lactate dehydrogenase (LDH), pyruvate dehydrogenase (PDH), and decrease in phospho-PFK-2/PFK-2 ratio). This activated the pentose phosphate cycle due to increased glucose-6-phosphate dehydrogenase (G6PDH) activity and NADPH levels. These results suggest that the formation of NADPH balances ROS-induced stress, reprograms metabolism from glycolysis to lipid oxidation, and thus compensates for the body's energy needs in the form of adenosine triphosphate (ATP) (14).

Moreover, the state of insulin signaling plays a significant role in the formation of ROS. When it is in a physiological state and well-regulated, the created ROS cause adipocyte differentiation which lasts for a short period time (15,16). However, in the state of adipocyte inflammation, due to the poorly regulated insulin signaling, chronic ROS production occurs, which is further aggravated by an excessive intake of nutrients. Based on this, it can be said that adipocyte inflammation induces strong ROS generation and thus contributes to the pathogenesis of IR associated with obesity (17). In addition to adipocytes, macrophages that accumulate in the adipose tissue also play an important role in generating ROS during the metabolism of excess nutrients. Therefore, it is important to understand oxidative stress during the various stages of obesity.

Excessive nutrient intake also contributes to the progression of IR through the catalytic activity of the enzyme NADPH oxidase (NOX) or through dysfunctional oxidative phosphorylation in mitochondria (18) produced by either adipocytes or macrophages. For the early stage of obesity, NOX plays an important role, since glucose and free fatty acids (FFA) are not metabolized to a greater extent by mitochondrial oxidation. Plasma membrane-bound NOX causes an increased ROS formation by electron transfer from NADPH to oxygen and superoxide formation. A superoxide is the first phase in the ROS-generating cascade that leads to the production of other forms of ROS / RNS. A superoxide can be converted into a less reactive but more durable particle, hydrogen peroxide, under the action of the enzyme superoxide dismutase (SOD) and later, under the action of this enzyme, a highly reactive hydroxyl radical is formed (19). Thus, ROS derived from NOX may be common mediators induced by both excess glucose and fatty acids in adipocytes where NOX activity increases proportionally with an increase in adipose tissue in the early stages of obesity (15). However, whether NOX-derived ROS alone can induce the occurrence of IR in adipocytes during the progression of obesity is not yet entirely clear. Today, there are significant indications that mitochondrial dysfunction is the cause of impaired insulin sensitivity in different cell types due to inadequate energy supply through insulin signaling (20).

Insulin signaling is of great importance for the regulation of secretion and the function of taught ROS in the state of obesity, which can serve to clarify the links between obesity and oxidative stress. In the preserved state of insulin signaling, the created ROS exhibit physiological effects, acting as secondary messengers and affect the adipocyte differentiation. However, in obesity with the presence of IR it comes to chronic ROS, which leads to numerous changes in the body. ROS is thought to promote insulin resistance by disrupting the signaling pathway of insulin receptor synthesis (21). Reactive radicals can stimulate protein kinase activity, as a result of which glucose is transported to adipocytes and FFA is increased, altogether leading to a change in energy balance. It is still unknown how different stages of obesity affect ROS production and whether or not they trigger IR (22).

Macrophages are potentially another important source of ROS in obese individuals. An increased production and accumulation of macrophages in parallel leads to the activation of immune cells that produce ROS derived from NOX, especially when

inflammation is the cause of fat accumulation. In an experimental study on mice loaded with a high-fat diet, it was shown that NOX deficiency contributes to the reduction of IR and the weakening of adipose tissue inflammation (23). This suggests that NOX may play a role in adipose tissue inflammation, but without evidence of whether ROS itself promotes IR and inflammation as adipose tissue increases and body weight increases. As obesity progresses, an essential site for ROS formation is the process of oxidative phosphorylation in the mitochondrial electron transfer chain. Initiated oxidative stress leads to an increased electron flow and the process of electron transfer in the mitochondrial chain is overloaded. Such mitochondria mainly produce superoxide, leading to a pro-inflammatory signaling cascade (24). In the IR state, glucose utilization is reduced, so energy for the adipocytes is expended from FFA. Their increase leads to increased ROS production, IkappaB kinase-nuclear factor-kappaB (IκB-NFκB) activation, and reduction of insulin signaling. The proinflammatory condition in this case causes a reduced number and reduced the functionality of mitochondria (25,26).

The excessive production of ROS (redox stress) contributes to oxidative damage, which also causes increased accumulation of fat, all resulting from an imbalance of prooxidans and antioxidants (24). This imbalance results in an increased lipid peroxidation in adipose tissue, which impairs the integrity of other metabolic tissues and may lead to liver, muscle and neurodegenerative diseases (27,28,29,30).

Redox stress is also involved in the process of adipogenesis in terms of impaired adipose tissue function during its accumulation. A weakened adipocyte development may result in their hypertrophy and hyperplasia with reduced oxygen supply (31). Thus, dysfunctional adipose tissue leads to the promotion of pro-inflammatory state and oxidative stress, so adipocytes begin to secrete specific molecules-chemokines. In the state of hypoxia caused by hypertrophy, adipocytes increase the secretion of numerous adipokines, such as macrophage migration inhibitory factor (MIF), matrix metalloproteinases (MMP2, MMP9), interleukin-6 (IL-6), interleukin1β (IL-1β), leptin and others (32). All of them can also act on immune cells, which in turn causes local and generalized inflammation that causes oxidative stress in obese people (33).

In that way, elevated leptin, which correlates with fat cell growth, affects both increased production of proinflammatory cytokines (tumor necrosis factor alpha (TNF-α), IL-6) and fatty acid oxidation in mitochondria (34,35). Elevated TNF-α values reduce eNOS expression in endothelial cells and strongly activate NADPH oxidase, resulting in the formation of ROS (36). In addition to macrophages, the presence of other immune cells in inflammation-mediated obesity has been noticed. The increased differentiation of these cells additionally generates a pro-inflammatory state and large ROS production occurs. The resulting ROS also acts on the increased activation of immune cells, which returns the whole process to the beginning and creates a vicious circle. This confirms a strong link between inflammation and oxidative stress, which can help to understand the pathogenesis of certain obesity-related diseases (37).

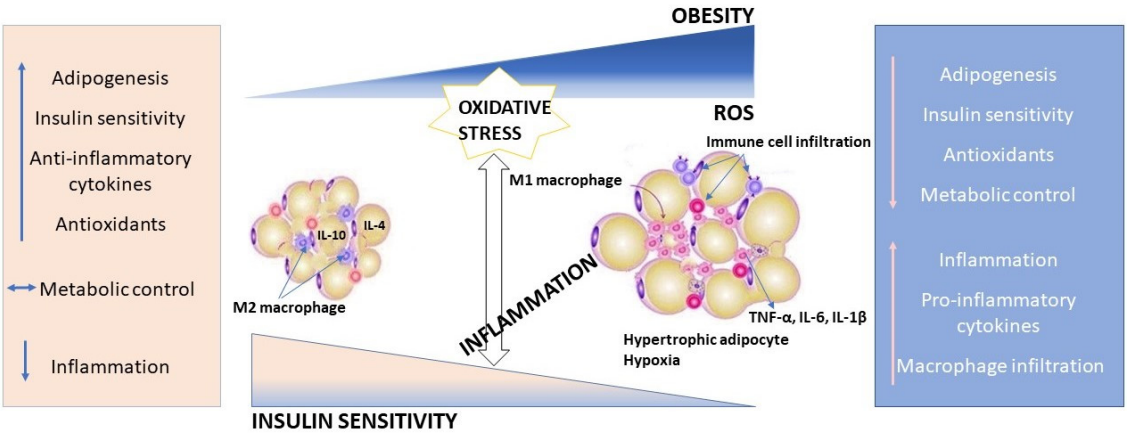

Figure 1. **The role of oxidative stress in obesity - resulting inflammation and metabolic dysregulation. The expansion of the adipose tissue with an increased ROS production causes hypertrophy of adipocytes that secrete chemoattractant molecules by infiltrating immune cells into the tissue. This adipocyte enhances the production of proinflammatory mediators (TNF-α, IL-6, IL-1β), which causes systemic inflammation. This environment negatively affects insulin signaling resulting in insulin resistance.**

Slika 1. **Uloga oksidativnog stresa u gojaznosti – rezultirajuća upala i metabolička disregulacija. Širenje masnog tkiva s povećanom proizvodnjom ROS-a uzrokuje hipertrofiju adipocita koji luče hemoatraktantne molekule infiltrirajući imunološke ćelije u tkivo. Ovaj adipocit pojačava proizvodnju prozapaljenskih medijatora (TNF-α, IL-6, IL-1β), što uzrokuje sistemsku upalu. Ovo okruženje negativno utiče na insulinsku signalizaciju što rezultira insulinskom rezistencijom.**

The most important biomarkers of oxidative stress in obesity

Oxidative stress in obesity causes numerous effects at the level of cell physiology. Numerous biochemical pathways and mechanisms of action are involved in the devastating effects of chronic obesity. Namely, in conditions when the accumulation of adipose tissue is present due to the formation of free radicals, there is modification and denaturation at the protein level, increased lipid peroxidation, disorders at the level of glutathione metabolism, changes in antioxidant enzyme activity and oxidative nucleic acid damage. Nowadays, there is a large number of different markers that can be used to monitor changes caused by oxidative stress at the level of affected cells, tissues, and organs, which can be used to quantify the progression of obesity. All of these markers can be divided into protein markers, lipid markers, and other types of biomarkers.

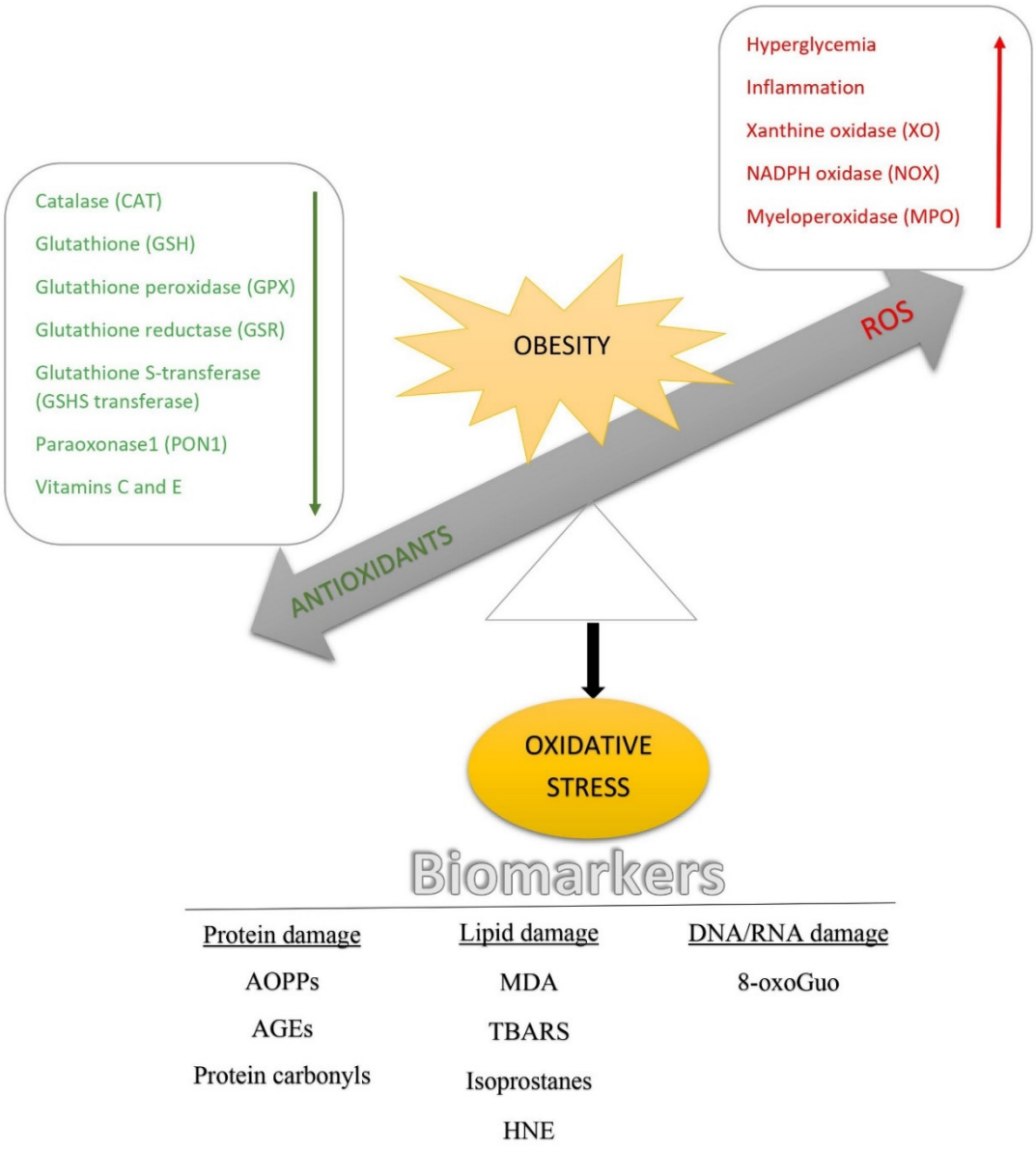

Figure 2. The most important biomarkers of oxidative stress in obesity
Slika 2. Najvažniji biomarkeri oksidativnog stresa u gojaznosti

ROS has been shown to react with some amino acids in vitro, causing modifications and denaturation at the protein level, which may further be responsible for the occurrence of oxidative stress. The state of obesity through the process of free radical production directly leads to oxidative degeneration at the level of protein structure. In vitro studies have shown that the enzyme *myeloperoxidase* (MPO) plays a significant role in the development of inflammation and oxidative stress. Its influence on the formation of oxidative stress is reflected in the increased reactivity of H_2O_2 and the formation of

hypochlorous acid, which creates oxidative products. This enzyme is considered to be a suitable marker for monitoring protein oxidation because it acts on protein modification by tyrosyl radicals.

Protein markers of oxidative stress, which play a role in obesity, include *advanced oxidation protein products* (AOPPs). They represent the overall status of proteins in cells. AOPPs are known to be proinflammatory and prooxidative substances that accumulate in obese patients with IR (38). They also affect an increased prevalence for endothelial dysfunction or cardiovascular disease in obese patients with metabolic syndrome (39).

Obesity leads to changes in the levels of the lipid profile of the organism, which makes the cells more susceptible to lipid peroxidation (40). An increased lipid peroxidation can also occur due to increased glycation of proteins in the IR state because glycated proteins can also serve as a source of free radicals. The peroxidation process produces highly reactive aldehydes which include malondialdehyde (MDA), acrolein, 4-hydroxynonenal (HNE), 4-oxo-2-nonenal (ONE) and isolevuglandine (IsoLGs). Numerous papers in this field indicate significant changes in lipid metabolism and structure present in obese patients. Increased concentrations of *malondialdehyde* (MDA) have thus been registered in obese patients with and without metabolic syndrome of both sexes where values increased with increasing BMI (41). MDA is created as a breakdown product and this mechanism involves the production of prostaglandins and endoperoxides derived from polyunsaturated fatty acids (PUFAs) with two or more double bonds. It is known that the increase in their concentration accompanies the state of obesity. Excess fatty acids enter the citrate cycle in which acetyl-CoA and NADH are generated, and therefore too much superperoxide production at the mitochondrial level. It is interesting to note significantly higher concentrations of *thiobarbituric acid reactive substances* (TBARS*)*, as a highly toxic end product of lipid peroxidation of fatty acids in erythrocytes, and in the serum of obese patients, with reduced activity of antioxidant enzymes (42,43). The peroxidation product of ω6-polyunsaturated fatty acids (ω-6 PUFAs), *4-hydroxynonenal* (4-HNE) is intensified in the state of oxidative stress where it has a highly toxic effect. 4-HNE is another lipid oxidation product that can be formed by non-enzymatic pathways. This molecule induces peroxide production and activates protein phosphorylation, JNK and p38 activity, and cJun and activator protein 1 (AP1) expression in macrophages, thus stimulating the cellular response to stress (44). Several studies have shown that an increased accumulation of 4-HNE in adipocytes contributes to the obesity-related lipolytic activation (45,46).

Isoprostanes (IsoPs), which are formed by non-enzymatic peroxidation of arachidonic acid, are associated with obesity and T2D (47). Obesity is associated with elevated levels of F(2)-isoprostane (F(2)-IsoP). However, it has been shown that this association may be inverse, where its elevated urinary values may predict a lower risk of obesity and diabetes because they affect the intensity oxidative metabolism. The strongest associations for total and abdominal obesity were found for F(2)-IsoP2 and F(2)-IsoP4, while the most pronounced inverse association was observed for F(2)-IsoP2 with weight gain during the 5-year follow-up period (48). The close association of abdominal obesity

and hyperglycemia with the growth of *8-iso Prostaglandin F2 alpha* (8-iso-PGF2α) has also been demonstrated, where it has been shown that enhanced production stimulates adipokine secretion and consequently leads to increased oxidative stress. In white adipose tissue, mitochondrial oxidative stress and ROS production are activated, which affects the endocrine and metabolic function of fat cells (49,50). Interesting biomarkers from this category are *adiponectin* and *leptin*, which are secreted from adipocytes and act through the CNS. Further analyses found a poor association between serum adiponectin levels with serum 8-iso-PGF2α in patients with type 2 diabetes (51). In addition to adiponectin levels, leptin levels are rising in obese diabetics and those with cardiovascular disorders (52).

Oxidative stress can lead to the damage at the level of cells and their dysfunction through the destruction of vital molecules, such as DNA, which lacks chemical stability. Oxidative damage caused by intracellular ROS results in modification at the level of DNA bases, cleavage within single-stranded or double-stranded molecules, and the formation of apurin/apyrimidine lesions, which are mostly toxic, meaning mutagen. In addition to DNA and RNA, it is subject to significant oxidative damage. The RNA oxidation marker *8-Oxo-2'-deoxyguanosine* (8-oxoGuo) has recently been identified as an independent predictor of mortality in patients with T2D (53). In a state of isolated obesity without present complications, an increase of only 8-oxoGuo (54,55) has been demonstrated, indicating that obesity itself increases oxidative stress as metabolic stress for mitochondria. It leads to a reduced mitochondrial respiratory chain efficiency, resulting in increased production of superoxide anions, hydrogen peroxide, and hydroxy radicals that oxidize RNA near mitochondria (56).

Antioxidants are natural or synthetic substances that successfully block free radicals in their destructive march on the body. They must be constantly regenerated in the body to establish a balance between them and free radicals. The highest percentage of total antioxidants in the body, which play an important role in the defense against ROS, are thiols. These are organic substances that contain a sulfhydryl group. Total thiols are composed of intracellular and extracellular thiols that exist in free form as oxidized or reduced glutathione or as protein-bound thiols. The most important representative of protein-bound thiols is albumin. In addition to their role in the fight against free radicals, thiols play a significant role in the process of detoxification, signal transduction and apoptosis. One of the most important representatives of thiol is *glutathione* (GSH). Glutathione/Glutathione disulfide (GSH/GSSG) redox pair is a traditional marker of choice in characterizing oxidative stress due to its high concentration and direct antioxidant role. It is a non-enzymatic antioxidant that maintains the thiol/disulfide redox state of the protein while eliminating peroxides. GSH contains a free thiol group that is capable of being formed to form a disulfide bond with another GSH molecule and other thiol-containing molecules. At the same time, GSH maintains the redox state of vitamin C, thus maintaining its antioxidant function (57,58). It is also a cofactor for a number of antioxidant enzymes, such as *glutathione peroxidase* (GPx), *glutathione reductase (GSR)* and *glutathione S-transferase* (*GSHS transferase)*. The role of these enzymes in the

development of diabetes complications is well-documented (59). All of these roles make the GSH system a central component of the cellular antioxidant response. GSH also protects erythrocytes from endogenous and exogenous free radical attacks and is an essential component of a highly efficient antioxidant system in erythrocytes. Given its role in erythrocytes, it is not surprising that its concentrations in erythrocytes are about 100 times higher than those in plasma. Therefore, it is this fact that indicates the potential for monitoring GSH concentrations in light of plasma antioxidant capacity (60). Thus, the decrease in GSH concentration correlates with the decrease in total blood, plasma and lymphoblast concentrations during the aging process, in rheumatoid arthritis, acquired immunodeficiency disorders, respiratory diseases, diabetes, hypertension, obesity and many other diseases. Its concentrations also correlate with other markers of oxidative stress (61). Glutathione reductase is an enzyme that uses NADPH and is responsible for producing sufficient amounts of reduced GSH. A drop in the activity of this enzyme will reduce the ability of cells to fight ROS.

An important endogenous antioxidant enzyme that catabolizes hydrogen peroxide produced by dismutation of superoxide is *catalase* (CAT). This enzyme converts hydrogen peroxides catalytically into water and oxygen and thus neutralizes the effects of said compound. In the case of enzyme deficiency, mitochondria of fat cells and beta cells of the pancreas are exposed to oxidative stress and produce excess ROS leading to cell dysfunction, and adipose tissue accumulation and worsening IR (62). In other words, this means that in a state of chronic obesity, insufficient activity of this enzyme leads to greater production of ROS and RNS and activation of oxidative stress pathways (63). The first line of defense against ROS-induced cell damage in the reaction of converting superoxide to molecular oxygen and peroxide is *superoxide dismutase* (SOD). In mammals, it occurs in three isoforms: SOD1 from the cytosol (Cu-Zn SOD1), SOD2 from the mitochondria and extracellular SOD3 (Cu-Zn SOD3). All three isoenzymes exert their biological effects partly through hydrogen peroxide, since it acts as a signaling molecule that activates processes such as hypertrophy, proliferation, and migration. A marked decrease in SOD activity occurs in intra-abdominal obesity with the presence of IR due to lipid peroxidation and progressive enzymatic glycation (64).

Paraoxonase 1 (PON1) belongs to the family of calcium-dependent hydrolases. It is mostly linked to high density lipoproteins (HDL). PON1 has paraoxonase, organophosphatase and lactonase activity, and hydrolyzes a number of substrates. PON1 has antioxidant activity, protecting HDL and low-density lipoprotein (LDL) from oxidation (65). It also contributes to the antiatherogenic and anti-inflammatory properties of HDL; degrades lipid peroxides, reduces HDL sensitivity to peroxidation, glycation, and homocysteinization, and increases the efflux of cholesterol from macrophages (66). Therefore, the action of this enzyme is closely related to diseases such as: T2D, hypercholesterolemia, cardiovascular complications and kidney disease (67,68,69).

PON1 activity is affected by direct glycation. It inhibits its activity, which reduces the protection of lipoproteins from oxidative stress present in T2D (70,71). Given the role of hyperglycemia in causing oxidative stress, due to reduced antioxidants and increased

ROS production, the protective effects of PON1 in preventing LDL peroxidation are thought to be more important in T2D patients than in non-diabetics (72). Some studies have shown that there is no difference in the reduction in activity of this enzyme when comparing normoglycemic patients, type 2 diabetics and those with impaired fasting glucose (73,74), which potentially indicates that a decrease in PON1 activity occurs later in diabetes than in phase IR.

Due to inconsistent results, as well as a small number of studies, for the monitoring of PON activity in obesity, measurement of PON1 activity such as (esterases and arylesterases) has been proposed. However, conflicting research results in obese patients without T2D and metabolic syndrome, and obese patients with metabolic syndrome but without T2D, still reappear.

Two separate studies have shown a negative correlation between PON1 activity with severe obesity and PON1 activity with metabolic syndrome in their results (75,76). Completely different results were presented by Tabur et al., in whom no differences in PON1 activity were observed between obese normoglycemic patients with and without metabolic syndrome (77), and Liang et al. who found elevated PON1 values in obese men with metabolic syndrome but without T2D (78). Due to the inconsistency of the results of previous research, it is impossible to explain with certainty the role of this enzyme in the monitoring of obese patients with and without associated metabolic disorders.

Xanthine oxidase (XO) is an enzyme that converts hypoxanthine / xanthine to uric acid in a superoxide-releasing reaction. High activity of this enzyme is found in metabolic disorders such as diabetes and obesity due to the production of superoxide which is cytotoxic (79). Numerous studies conducted in recent years have indicated an increase in the activity of this enzyme in both obese and T2D patients (80,81). In a study by Harisson et al. conducted in adolescents, a weight loss of 5 kg has been shown to lead to a 9.8% decrease in XO activity with a decrease in uric acid (82). Furthermore, xanthine oxidoreductase (XOR) has also been linked to the pathogenesis of metabolic syndrome and obesity through oxidative stress and ROS-induced inflammatory response. Serum XOR levels are associated with triglyceride/cholesterol ratio, HDL, fasting glycemia, fasting insulin, and IR index. In addition, XOR is involved in the differentiation and adipogenesis of pre-adipocytes, and together with uric acid they play a role in cell transformation and proliferation, confirming their contribution to metabolic syndrome. However, in some circumstances XOR and uric acid may have antioxidant protection. The dual role of both XOR and uric acid explains the contradictory results obtained with XOR inhibitors and suggests caution in their therapeutic use (83,84).

Vitamins can also be important in the detoxification of free radicals. In obesity, vitamins C and E are linked to suppress the accumulation of adipose tissue, which with their antioxidant properties also act to suppress the complications caused by this condition. The beneficial effects of vitamin C on the mechanisms associated with obesity are reflected in the reduction of IR, inhibition of leptin secretion in adipocytes and enhanced lipolysis of fat cells. These effects result in reduced glycolysis and proinflammatory response (85), and all together make it a vitamin with good antioxidant

properties. Vitamin E also works to improve the expansion of adipose tissue by suppressing the inflammatory and fibrotic process, which causes improved insulin sensitivity. The mechanism may involve, though not exclusively, the antioxidant action of vitamin E in metabolic improvement of obesity (86).

Conclusion

Obesity is a serious public health challenge in the 21st century. The risk of many diseases, including T2D, cardiovascular disease, neurodegenerative disease, autoimmune disease, and cancer, is dramatically increased in obese patients. In recent years, it has been recognized that oxidative stress may be a mechanical link between obesity and the related complications, as oxidative stress causes tissue damage through changes in cellular structures. Overexpression of oxidative stress, along with a lack of antioxidant defenses, may explain the pro-oxidative environment observed in obesity. This is reflected in changes in regulatory factors of mitochondrial activity, changes in the concentration of inflammatory mediators associated with an increased number and size of adipocytes, stimulation of lipogenesis, stimulation of preadipocyte differentiation to mature adipocytes, and regulation of energy homeostasis. Despite numerous data on biomarkers of oxidative stress in obesity, there is a need to further examine the relationship between free radicals and antioxidants in obesity and its complications. Of particular interest are studies of the mechanisms by which oxidative stress stimulates the development of obesity.

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Oksidativni stres i gojaznost

Maja Malenica[1]*, Neven Meseldžić[1]

[1]Univerzitet u Sarajevu - Farmaceutski fakultet, Katedra za Farmaceutsku biohemiju i laboratorijsku dijagnostiku, Zmaja od Bosne 8, 71000 Sarajevo, Bosna i Hercegovina

*Autor za korespondenciju: Maja Malenica, e-mail: maja.malenica@ffsa.unsa.ba

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Kratak sadržaj

Gojaznost je bolest prekomernog nakupljanja masnog tkiva zbog povećanog energetskog unosa koji je u nesrazmeru s potrošnjom energije u organizmu. Tako nakupljeno visceralno masno tkivo kod gojaznih osoba povećava rizik od razvoja niza metaboličkih i kardiovaskularnih bolesti. Poremećaji kao što su dijabetes, dislipidemija, inflamacija, disfunkcija endotela i mitohondrija mogu doprineti nastanku oksidativnog stresa, što je posebno izraženo kod abdominalnog tipa gojaznosti. Gojaznost sama po sebi može indukovati sistemski oksidativni stres kroz različite biohemijske mehanizme. Iako se ROS generiše u velikom broju ćelija, značajnu ulogu u njihovoj unutarćelijskoj proizvodnji zauzimaju mitohondrije, kroz proces oksidativne fosforilacije respiratornog lanca i u reakcijama oksidacije masnih kiselina u različitim fazama gojaznosti. Oksidativni stres predstavlja jedinstvenu vezu između različitih molekularnih poremećaja koji su prisutni u razvoju insulinske rezistencije, koja ima ključnu ulogu u patogenezi i progresiji hroničnih metaboličkih, po svom karakteru proinflamatornih oboljenja. Na progresiju insulinske rezistencije utiče i inflamacija, koja može biti i uzrok i posledica gojaznosti. Inflamacija predstavlja jednu od manifestacija oksidativnog stresa, jer putevi u kojima se stvaraju medijatori inflamacije bivaju indukovani oksidativnim stresom. Ovaj pregled ima za cilj da istakne nedavna otkrića o ulozi oksidativnog stresa u patogenezi gojaznosti, uz poseban osvrt na mehanizme koji objašnjavaju njegov nastanak.

Ključne reči: oksidativni stres, insulinska rezistencija, inflamacija, biomarkeri

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