sciendo Revista Română de Medicină de Laborator 2024;32(2):135-142 REVIEW
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# The role of nitro oxidative factors in metabolic dysfunctions: A link between severe obesity and weight-loss treatment – a narrative review

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## ABSTRACT

**Introduction**: Metabolic syndrome (MS) is linked to oxidative stress and intracellular redox imbalance, both triggered by chronic inflammatory conditions. The aim of our research was to figure out if bariatric surgery changes the production of free radicals in obese people. In addition, the relationship between metabolic syndrome(MS) and associated conditions is represented by oxidative stress (OS) and intracellular redox imbalance, both of which are induced by the chronic inflammatory conditions that define MS.

**Methods**: The literature search was conducted on PubMed, Cochrane Library, and ScienceDirect, using terms related to severe obesity, nitro-oxidative factors, pro-inflammatory status and reactive oxygen species. Six studies were included. We included papers published till 2022, with a concentration on more recent publications (January 2019 to December 2022).

**Results**: Studies that analyzed the status of the patient after bariatric surgery at 1, 2, 3, 6, 12 months were included in the review, regarding inflammation: CRP levels,IL-6, and regarding oxidative stress: MPO serum activity, blood plasma proteins: dityrosine, kynurenine, glycophore, amyloid and Amadori products, had been found strongly statistically significant decreased at each periodic analyze, the same thing applied to regulatory hormones such as leptin, and due to the fact that these patients have the possibility to keep their weight stable for a longer period, all these factors kept their levels low even 4 years after the intervention.

**Conclusion**: Bariatric surgery is an efficient and quick solution in increasing the quality of life.

**Keywords:** bariatric surgery, oxidative stress, inflammation biomarkers, severe obesity

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## INTRODUCTION

In light of all the warning signs raised by experts over the past two decades, the obesity epidemic is yet another major concern for the global health situation. Obesity is proving to be the root cause of a significant worsening in the health status of those with the condition, leading to a severe decline in their quality of life, but above all, it is the most common cause of morbidity and mortality. In terms of the complexity of the pathophysiological mechanisms involved in this condition, there is evidence of a significant interaction between genetic abnormalities and environmental factors[1]. An overweight person develops a systemic overload of the organism, a phenomenon associated with complications such as cardiovascular disease, type 2 diabetes, musculoskeletal complications, and certain cancers. In terms of understanding the seriousness of this pathology, there

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is a need to act to overcome the whole dramatic clinical picture generated by this pathology, but also to reduce the occurrence of premature death in these patients[2].

Assuming that fast and significant weight loss would be associated with the reduction of inflammatory and oxidative stress marker levels, we investigated the lately available literature regarding this subject. Oxidative stress occurs when cellular metabolism is disturbed by oxidized lipids and proteins, eventually leading to cell death by apoptosis and necrosis, through overproduction of reactive oxygen (ROS) and nitrogen (RNS) species. Therefore, several antioxidant systems protect cells in aerobic organisms, not only through ROS-induced oxidation inhibition but also by biomolecule repairment of some forms of oxidative disturbances. Some of the most important blood antioxidants include alpha lipoic acid, SOD, CAT, GPx, GR, GSH and UA [3].

Related to obesity, various inflammatory markers have been consistently associated with both obesity and the risk of poor outcomes in obesity-associated conditions, implying that an ongoing poor inflammatory response may be a potentially modifiable risk factor. There are several causes of inflammation in obesity. Dietary excess calories are a major cellular oxidative stress factor, leading to an excess of metabolic by-products through mitochondrial and peroxisomal oxidation of fatty acids, thereby causing higher levels of reactive oxygen species, hydrogen peroxide and nitric oxide, all of which can be harmful to cells. Consequently, increased metabolic processing of extra calories is likely to directly fuel cellular inflammatory processes. The inflammatory factors have a major part to play in a range of biological pathways, spanning from alterations in body temperature to local vascular responses [4].

The primary aim of the study was to explore the interrelationships between reactive oxygen species (ROS), severe obesity, and metabolic syndrome. Additionally, as a secondary endpoint, it hypothesized as to whether the process of weight loss, in particular, subsequent to bariatric procedures, is likely to have been a part of decreasing obesity-related proinflammatory status and comorbidities. The breakdown of former paradigms coupled with a fresh foundation of knowledge, establishes a solid ground in terms of understanding the condition and establishing strategies for treatment and prevention.

### Search strategy

A survey conducted by two researchers IRM and MS over March-April 2023 focused on severe obesity, nitro-oxidative factors, oxidative stress, pro-inflammatory status, reactive oxygen species, and combinations thereof using PubMed, Cochrane Library and Science Direct electronic databases. The study included recent publications, prospective studies, reviews, systematic reviews, comparative studies, and RCTs. The inclusion criteria were relevant data, comparative data, and English articles.

The 10-question CASP checklist was used to critically appraise 1898 articles, focusing on 8 publications after removing duplicates, abstracts, and non-English studies, excluding articles with insufficient data, primary results, comparative data, or studies in foreign languages.

## THE IMPACT OF OXIDATIVE STRESS AND INFLAMMATION SYSTEM IN SUBJECTS WITH MORBID OBESITY

The pro-inflammatory status of obesity is a well-known phenomenon. The extra calorie intake is a cellular oxidative stressor through which excess metabolic by-products of the mitochondrial and peroxisomal oxidation of fatty acids result in increased reactive oxygen species (ROS), hydrogen peroxide (H2O2), and nitric oxide (NO), which in more substantial quantities are cell toxic [5]. Elevated formation of the different ROS, denoted as ”oxidative distress”, leads to molecular damage in proteins, lipids, and DNA. The major agent signaling through specific protein targets, hydrogen peroxide, engages in metabolic regulation and stress responses to support cellular adaptation to stress and a changing environment [6]. Nitric oxide is responsible for effects such as decreasing blood pressure, causing vasodilation, and stimulating the release of certain hormones like insulin and human growth hormone (HGH) [3]. NO deficiency reflected in endothelial dysfunction is a specific characteristic of insulin-resistant conditions and is a main process linking insulin resistance and atherosclerotic cardiovascular disease [7]. These oxidants have a major role in physiology and disease, including the cardiovascular, immune, and nervous systems, skeletal muscle, ageing, and cancer as well as metabolic adjustment [4].

The capacity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) decreases with the increase in fat storage capacity [8]. In addition to the proliferation, adipocytes can store excess fuel in lipid vacuoles, leading to hypertrophy and, eventually inducing inflammatory processes through the release of their internal content. Fat infiltrates the adipose tissue (AT) and other metabolically relevant organs like the liver, skeletal muscle, or pancreas resulting in a local production of adipokines and pro-inflammatory cytokines [9].

Obesity patients’ inflammatory tolerance is compromised, leading to increased inflammatory mediators and decreased anti-inflammatory factors, promoting hyperlipidemia and preventing insulin-activated lipogenesis.

Obesity is linked to cognitive decline due to oxidative stress and inflammation. High leptin levels in serum trigger adipose tissue to release pro-inflammatory factors like IL-1, IL-6, and TNF-alpha. These factors modulate hippocampus-dependent memory and brain function, leading to inflammatory microgliosis. Over-release of IL-6 increases vascular endothelial growth factor (VEGF), suppressing occludin and increasing BACE1 enzymes in the brain. TNF-α affects hippocampal memory function and can inhibit long-term potentiation (LTP), a synaptic interface between hippocampal neurons and brain memory [10].

## EFFECTS OF BARIATRIC SURGERY ON PATIENTS WITH MORBID OBESITY

Bariatric surgery (BS) was shown to be remarkably effective for the treatment of obesity and its comorbidities. BS has the potential to achieve long-term weight control and has proven to be superior when compared to non-surgical treatments in terms of quality of life, despite the risks of severe postoperative complications [11].

The major weight-loss mechanisms for these procedures were considered to be restriction (VSG, RYGB and OAGB), malabsorption (OAGB and RYGB), and neurohumoral factors (RYGB and OAGB > VSG). More recent theories propose a variety of mechanisms, including effects on the regulation of energy expenditure; glucose homeostasis; insulin secretion and sensitivity; changes in appetite regulated by gut hormones and the central and peripheral nervous systems; food preferences and alterations in bile acid physiology; intestinal hormone secretion and the gut microbiome [12].

Subsequent to bariatric surgery, shifts that occur in body composition, particularly a sustained loss of fat mass (FM), are often related to an inevitable loss of fat-free mass (FFM). Losing FFM is likely unwanted when excessive, as non-adipose tissues provide most of the resting metabolic rate, regulation of core body temperature, maintenance of skeletal integrity, and upkeep of function and overall quality of life as the body is ageing [13].

However, sustained and durable weight loss has been proven challenging to achieve, especially as the gap between body weight excess and a normal BMI becomes higher. Front-line treatment, such as lifestyle modifications, including caloric intake reduction, manipulation of daily macronutrient ratios, and varying levels of physical training intensity and duration, accompanied or not by naturist or drug therapy designed to help in weight loss are sometimes not enough. In these cases, various types of surgical weight loss procedures, to name the most popular, Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB), one-anastomosis gastric bypass (OAGB), vertical sleeve gastrectomy (VSG), or biliary pancreatic diversion (BPD) could be taken into consideration [12].

While surgical techniques and post-operative nursing have been optimized, physicians and surgeons alike must continue to monitor bariatric patients for possible medical and surgical-related complications and manage them as necessary. In addition to a solid emotional support group, a multidisciplinary team consisting of surgeons, internists, dieticians and psychologists can be crucial to achieving the best results from weight loss surgery [14].

## CORRELATIONS BETWEEN OBESITY AND PRO-INFLAMMATORY STATUS

Neutrophils and lymphocytes, crucial for innate and adaptive immunity, are recruited to injury sites, including inflammation, and are used as prognostic factors in inflammatory diseases. A survey of 1747 adults over 50 emphasized the significance of neutrophil/lymphocyte ratio (NLR), a new biomarker. NLR was measured from blood samples, with gender differences in anthropometric measurements [15].

Choromanska et al. studied the antioxidant barrier and oxidative damage by comparing redox homeostasis parameters between a group of 65 grade 3 obesity patients with MS (OB+MS), who underwent bariatric surgery with a control group of 33 healthy individuals. Regarding inflammation, CRP levels at baseline in obese morbid with metabolic syndrome (OB+MS) patients had strongly significantly higher values compared to lean control. At 6 and 12 months post-BS, CRP levels appeared to be strongly significantly higher in the OB+MS group compared to the OB group, while strongly significantly lower levels were found 12 months post-BS compared to the same groups before surgery.

Regarding oxidative stress, in Choromanska et al study, the activity of the enzymatic oxidants: serum superoxide dismutase (SOD), and serum glutathione reductase (GR) are statistically significantly lower, while uric acid (UA) is statistically significantly higher compared to healthy lean control in comparison between study populations (OB and OB+MS) with the healthy control group [16].

Moreover, negative correlations between CAT and glucose, and GPx and HOMA-IR score assessment [($R = -0.432$; $p = 0.014$), respectively ($R = -0.375$; $p = 0.049$)], while positive correlations between GR and TG, UA and BMI, and UA and HDL [($R = 0.367$; $p = 0.046$), ($R = 0.371$; $p = 0.04$), respectively ($R = 0.507$; $p = 0.008$)] were found.

Choromanska et al. [17] evaluated protein glycoxidation and nitrosative damage in 50 patients with severe

obesity before and after laparoscopic sleeve gastrectomy compared to healthy controls aged 28-56.

Myeloperoxidase (MPO) is a heme-containing peroxidase expressed mainly in neutrophils and monocytes, which catalyzes the formation of reactive oxygen intermediates. The MPO system plays an important role in microbial killing by neutrophils and is a local mediator of tissue damage and the resulting inflammation in various inflammatory diseases, reasons for which it might be considered an important therapeutic target in the treatment of inflammatory conditions [16].

Morbidly obese patients had significantly higher myeloperoxidase (MPO) serum activity before and after bariatric treatment compared to lean controls in Choromanska B study. However, the activity of MPO slightly diminished after 12 months. Morbidly obese patients also had higher oxidative modifications of blood plasma proteins, including dityrosine, kynurenine, glycophore, amyloid, and Amadori products. The plasma content of dityrosine increased before and after bariatric surgery, while the content of kynurenine decreased at 6 and 12 months. The content of amyloid also decreased at 6 and 12 months. Furthermore, the concentration of Amadori products in morbidly obese patients was higher than in lean controls before and 1 month after BS. A decrease was observed at 3 and 12 months after surgery. The study suggests that morbid obesity may contribute to the development of oxidative stress and other health issues [17].

Regarding nitrosative stress, higher plasma concentration of total NO, peroxynitrite, S-nitrosothiols as well as nitrotyrosine in morbidly obese patients before BS [(p <0.0001), (p <0.0001), (p <0.0001), (p <0.0001)], as well as after laparoscopic sleeve gastrectomy at 1, 3 and 6 months [(p <0.0001); (p < 0.0001); (p = 0.0012)], had been observed, while the other three progressively significantly decreased at 6 and 12 months [(p = 0.003; p = 0.0153)], at 3, 6 and 12 months [(p = 0.0154); (p = 0.0001); (p <0.0001)] and at 6 and 12 months respectively [(p <0.0001); (p<0.0001)] after bariatric treatment [17].

The study found significant associations between serum insulin concentrations, plasma peroxynitrite, Amadori products, plasma total thiols, and insulin resistance assessment score (HOMA-IR). Plasma kynurenine had a positive association with RBC and AST, but a negative association with diastolic blood pressure (DBP). Plasma N-formyl-kynurenine was also negatively associated with DBP and LDL. Plasma tryptophan and RBC, plasma Amadori products and BMI, serum MPO and BMI, and plasma S-nitrosothiols and UA strongly correlated. Dityrosine content also correlated negatively with weight loss. These findings suggest that Amadori products can potentially improve blood sugar levels and overall health.

Choromanska's research highlights the increased plasma glyco-oxidative products, protein oxidation, and nitrosative/nitrative stress in MS patients compared to lean controls. They found that redox homeostasis improved after bariatric surgery and nitrosative/nitrosative stress plays a key role in the development of morbid obesity [17].

Chemerin levels, an inflammatory chemokine, in morbidly obese patients before and at 6 months after BS, were also evaluated by Catoi et al. [19], along with hsCRP, TNF-α, NOx, TOS, TAR, and OSI. Conclusive results show that hsCRP, NOx, and TOS differed strongly significantly, while TAR and OSI differed significantly higher in the morbidly obese group compared to the control group [18].

Moreover, 6 months after BS, they noticed significant changes in hsCRP (p = 0.044) with a decrease of 42.28% comparing the morbidly obese group with baseline values, respective OSI (p = 0.041) with a decrease of 31.81% comparing the same groups, while no significant changes were observed between the same groups as far as chemerin (p = 0.605), TNF-α (p = 0.287), NOx (p = 0.137), TOS (p = 0.158), and TAR (p = 0.563) are concerned.

Considering that chemerin is an inflammatory marker, a decrease in its values was presumed, but its circulating levels which were increased at baseline compared to the healthy patients group did not decrease statistically significantly with the decrease of BMI, thus no correlation could be demonstrated. Although comparing the two groups of MHMO and MUHMO in terms of nitro-oxidative markers in their other study, chemerin and Nox, have significantly lower levels in the first group compared to the second, while chemerin levels are identified as possible predictors for MS in the MHMO [19]. However, changes in chemerin correlated with TAR levels [18].

Consistent with these data, other research studies identify a positive correlation between serum chemerin and CRP levels [20,21], with no correlation with BMI and fat mass. A study on chemerin levels related to inflammatory diseases made by Gonzalez-Ponce et al on 210 patients with Rheumatoid Arthritis, using a Pearson correlation test, identified a positive correlation between serum chemerin and CRP levels (r = 0.14; p = 0.04), but no correlation was observed with BMI (r = 0.043, p = 0.535) and fat mass (%) (r = 0.098, p = 0.158) [20]. Another study investigating associations between serum Chemerin and clinical outcomes, as a prognostic indicator in Chronic Heart Failure, is the study made by Zhou et al on 834 patients with chronic heart failure in a prospective cohort study using multivariate Cox regression analysis. Among the results, a positive correlation between serum chemerin and hsCRP levels (p <0.0001),

as well as with Metabolic Syndrome components such as Hypertension (p < 0.001), Diabetes mellitus (p = 0.001), Hyperlipidemia (p = 0.002) or eGFR (mL/min/1.73m$^2$) (p = 0.005) was identified. According to these data, chemerin and inflammation may be associated, independently of BMI and fat tissue [21].

Min et al aim to evaluate the effects of BS on metabolic regulatory hormones (adiponectin, leptin), proinflammatory cytokines (CRP, IL-6, IL-10) and measures of global plasma oxidative stress (TBARS and TOS) evaluated at 1 and 6 months, and 4 years respectively, after weight-loss surgery. Regarding adipokines and inflammatory cytokines, compared to baseline, statistically significant decreases were seen 4 years post-BS in leptin, CRP, and IL-6 levels, while IL10 and adiponectin presented no significant modifications. A progressive decrease was seen in every evaluated time frame from baseline in Adiponectin and Leptin levels, while the same pattern goes on in the case of CRP, IL6 and IL10, but with some fluctuations [22].

At 4 years after weight-loss surgery, both fasting and 120 min TOS significantly increased [(+35%, p = 0.042); (+19%, p = 0.026)]. Still, fasting and 120 min TBARS did not show any significant changes in any evaluated time frame. Moreover, strongly significant positive correlations between leptin and weight, respectively leptin and BMI [(r=0.656, p=0.002); (r=0.734, p=0.001)], suggested that a greater reduction in leptin is associated with a greater reduction in the heaviness of an individual, while a negative correlation between 120-min TOS and fasting plasma glucose with a positive correlation between 120-min TBARS and HbA1c [(rs=−0.66, p=0.004); (r=0.506, p=0.045)] suggested that a greater reduction in plasma sugar levels is associated with lower oxidative stress markers.

Regarding oxidative stress, while Catoi et al. observed no change in global measures (Nox, TOS, TAR and OSI), 6 months after SG [19], Min et al. report a significant increase of TOS, with no significant change of TBARS at four years after BS [22].

During the follow-up period, surgical patients showed a decrease in HOMA-IR, C-peptide, and ghrelin levels, while adiponectin and GLP-1 levels increased. Pro-inflammatory and oxidative stress markers were assessed, and hsCRP levels decreased in surgical patients. Homocysteine levels remained unchanged in both groups, suggesting that the surgical group's oxidative stress markers were unfavorable compared to dietary and intensive medical treatment [22].

Metere's study found that the generation of 3-carboxy-proxy1 radical (CP) is linked to an increase in pro-oxidant species. To combat this, antioxidant enzymes like SOD and DTPA were tested. However, no significant inhibition of CP concentration was observed with these compounds. The study also found that SOD may increase CP radical concentration, suggesting that increased CP concentration may not reflect increased oxygen production. The study suggests that electron paramagnetic resonance (EPR)-spin probe analysis is a reliable technique for identifying the main oxidant species responsible [23].

Tozzo et al. observed in a review article that six years after RYGB, 45% (n = 9) of patients stopped using prescribed vitamin supplements postoperatively. Both reduced glutathione(GSH) and catalase(CAT) appeared to be not significantly different in the bariatric group(BG), compared to the control group (CG) at M0 (p = 0.119 and 0.644, respectively). In BG, GSH levels decreased by 6 months (p = 0.030), however, they recovered to M0 values after 72 months (p = 0.627). In comparison to M0 at M72, CAT activity was unchanged (p = 0.881). Notably, levels of thiobarbituric acid (TBARS), that were significantly higher in BG compared to CG at M0 (p < 0.001), suffered a substantial decline from M12 to M24 (p < 0.001 and p = 0.004, respectively), but increased at M72, recovering to values similar to those found at M0 (p = 0.114). Total cholesterol and triglyceride concentrations both dropped substantially after 72 months (p = 0.003 and p < 0.001, respectively) [24].

## CONCLUSION

Bariatric treatment preserves long-term weight loss and lowers the risk of several MS co-morbidities, not only by improving the metabolic status of morbidly obese people but also by prolonging their lives and enhancing their quality of life. It is well known that overall improvement in metabolic indices leads to an amelioration of inflammation-driven dysfunction directly proportional to the percentage of fat tissue decreased. Findings suggest that cardio-metabolic health cannot be achieved by persisting obesity.

This study explores the role of obesity in metabolic syndrome changes and suggests that bariatric surgery may provide a biochemical link to the numerous clinical links between obesity and inflammation-related diseases.

## ABBREVIATIONS

AGB – Adjustable gastric banding

AT – Adipose tissue

BPD – Biliary pancreatic diversion

BMI- Body Mass Index

BS – Bariatric surgery

CAT- Catalase
CRP – C reactive protein
GPx – Glutathione peroxidase
GR – Glutathione reductase
GSH – Antioxidant glutathione
hsCRP – High sensibility protein C reactive
HC – Hip Circumference
$H_2O_2$- Hydrogen peroxide
HOMA-IR – Homeostatic model assessment for insulin resistance
HDL – High-density lipoproteins
HGH – Human growth hormone
MPO – Myeloperoxidase
MS – Metabolic syndrome
NO – Nitric oxide
NOx – nitrite and nitrate
OAGB – One-anastomosis gastric bypass
OB – Obese subject
OSI- Oxidative stress index
RNS – Reactive nitrogen species
ROS- Reactive oxygen species
RYGB – Roux-en-Y gastric bypass
TAR – Total antioxidant response
SOD – Superoxide dismutase
TOS – total oxidant status
TNF-alpha – tumor necrosis factor- alpha
TG – Triglycerides
UA – Uric acid
VAI – Visceral Adiposity Index
VSG – Vertical gastrectomy surgery
WC- Waist Circumference
WHtR – Waist-to-Hip Ratio

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## AUTHORS' CONTRIBUTION

Conceptualization, I.R.M., M.S.; methodology, validation, I.R.M., formal analysis, I.R.M.; resources, M.S.; data curation, M.S.; writing—original draft preparation, I.R.M., M.S.; writing—review and editing, I.R.M., F.G.B., A.H.; visualization, D.T.S., A.R.; supervision, N.R.M. All authors have read and agreed to the published version of the manuscript.

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## INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki: and approved by the Ethics Committee of Targu Mures Emergency County Hospital, Romania (protocol code 3570, on 19 February 2021).

## CONFLICT OF INTEREST

None to declare.

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