

## INSULIN RESISTANCE AND OXIDATIVE STRESS IN ELDERLY WOMEN<sup>1</sup>

### *RESISTÊNCIA À INSULINA E ESTRESSE OXIDATIVO EM MULHERES IDOSAS*

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#### ABSTRACT

The change in eating habits as a consequence of shortage of time and ingestion of processed foods, in association with a sedentary lifestyle, has increased the prevalence of obesity in all age groups of the population. This work was aimed at finding studies in the literature which correlate insulin resistance and oxidative stress in a population of elderly women. An integrative review of the literature with an exploratory approach was the methodology employed to conduct the work. Electronic data collection was performed in the PubMed database from October to November 2017. The MeSH terms used in the PubMed search builder were *insulin resistance-oxidative stress-elderly women*, joined by the connective *and*. The search resulted in 55 full-text papers, out of which eight met the criteria established for the present assessment. The study findings indicated that the body composition has a significant influence on the target audience regarding the occurrence of comorbidities, among which is the excessive abdominal fat, combined with a poor diet and inactivity, as a possible cause of Oxidative Stress. As a result, conditions such as Insulin Resistance, arterial hypertension and physiological changes are triggered. It may be concluded that the search to lower or maintain body weight, regular physical activity and proper diet can positively influence the reduction of the reactive oxygen species, obesity and Insulin Resistance. However, studies on this topic may help to understand the interaction between oxidative stress and insulin resistance.

**Keywords:** *catalase, aging, insulinemia.*

#### RESUMO

*A mudança nos hábitos alimentares em decorrência da falta de tempo, os alimentos industrializados, aliados ao sedentarismo tem elevado a prevalência da obesidade em todas as faixas etárias da população. O objetivo deste estudo é encontrar na literatura, trabalhos que correlacionem a resistência à insulina e o estresse oxidativo em uma população de mulheres idosas. Revisão integrativa da literatura com um caráter exploratório. A coleta de dados ocorreu na base eletrônica do PUBMED. Utilizou-se os mesh terms: Insuline Resistance, Oxidative Stress e elderly,woman conectados pelo Builder: AND. A busca resultou em 55 artigos completos, dos quais oito atenderam as características desse estudo. Os resultados demonstraram que a composição corporal, no público-alvo, tem influência significativa no surgimento de comorbidades, dentre eles a elevada presença de gordura abdominal, aliada a dieta inadequada e ao sedentarismo como possíveis causas do estresse oxidativo. Como consequência, desencadeando quadros de resistência à insulina, hipertensão arterial e alterações fisiológicas. Conclui-se que a busca pela redução ou manutenção do peso corporal, a atividade física regular e uma dieta adequada, podem interferir de maneira positiva na redução das espécies reativas de oxigênio, da obesidade e da resistência à insulina.*

<sup>1</sup> Work developed in the Master of Health and Life Sciences; part of the Masters dissertation.

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*Entretanto, mais estudos sobre essa temática podem auxiliar na compreensão dessa interação entre o estresse oxidativo e a resistência à insulina.*

**Palavras-chave:** *catalase, envelhecimento, insulinemia.*

## INTRODUCTION

With the increased obesity and reduced practice of physical activity, several disorders such as the Metabolic Syndrome (MetS) have stand out in the last decades due to their high prevalence in the general population, especially in the older age groups; these include people aged 60 years and over in Brazil, according to the federal law n. 10.741 of 1 October 2003 (BRASIL, 2003). As aging is a dynamic process in which morphological and physiological alterations occur at all levels of the organism (LEITE, 2012), the latter is led to a progressive decline in the physiological capacity and to a reduced ability to respond to environmental stress. The elderly population is thus more susceptible and vulnerable to diseases.

Endothelial dysfunction, insulin resistance (IR), dyslipidemia and increased abdominal circumference are commonly seen in MetS patients; they may be associated to numerous other risk factors, such as lifestyle, unhealthy diet, smoking, physical inactivity and genetic inheritance, for example.

Resistance to the action of insulin has an important role in the association of these risk factors for the development of cardiovascular diseases, diabetes and other comorbidities, since insulin acts in the dynamic maintenance of glucose homeostasis (TELES, 2015). Besides triggering physiological and morphological alterations in the cardiovascular and neural systems, homeostatic imbalance elevates the risk of mortality. Another type of event that may be affected by the homeostatic imbalance is the production and metabolism of the reactive oxygen species (ROS) and reactive nitrogen species (RNS), which may generate oxidative stress (OS).

In the light of the above, this work was aimed at finding studies in the literature which correlate insulin resistance (IR) and oxidative stress (OS) in a population of elderly women.

## MATERIAL AND METHODS

This study employed an exploratory approach, since it is an integrative literature review. PubMed has served as the tool for electronically searching for articles, and the search builder consisted of the following MeSH terms, connected by the word *and*: *insulin resistance, oxidative stress, elderly women*.

The inclusion criteria used to select the articles were: online full-text articles; published in the past 10 years; samples consisting of women over 60 years old; written in Portuguese, English and Spanish; and presenting the searched theme and the specific population. Works with the following

features were excluded from the study: literature reviews; sample composed of non-elders or men; *in vitro* investigations; not available in full.

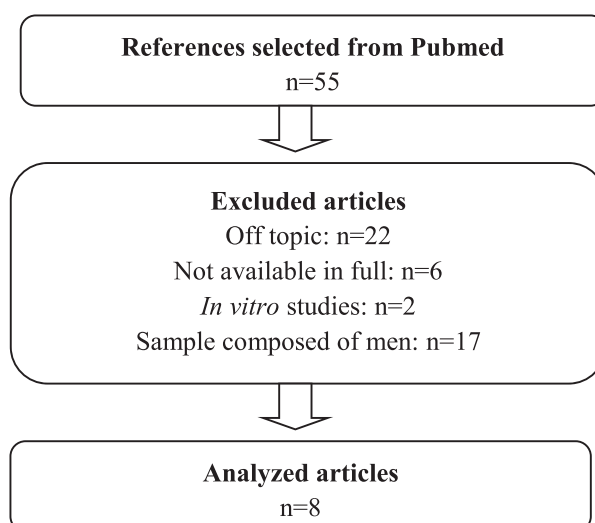
After retrieving the articles from PubMed, a screening of the citations and abstracts was performed to verify whether the studies met the inclusion criteria. Subsequently, the articles were thoroughly read and the following information was registered: name of first author, year of publication, aim, sample and results.

## RESULTS AND DISCUSSION

Fifty-five articles were selected in the first screening of the PubMed citations, out of which only eight met the criteria established for the current study.

Figure 1 shows a flowchart of the search strategy and the selection of the articles which were included in this assessment.

**Figure 1** - Flowchart with the strategy used to select the articles for the current assessment.



After selecting eight out of the retrieved articles, the aim and the main results were analyzed (Figure 2).

**Figure 2** - Characteristics Of Studies.

Title	Author	Aim	Main Results
The relationship between circulating neutrophil gelatinase associated lipocalin and early alteration of metabolic parameters is associated with dietary saturated fat intake in non-diabetic Korean women.	Gy <i>et al.</i> (2017)	To examine the relationship between serum neutrophil gelatinase-associated lipocalin (NGAL) and early alteration of metabolic parameters in non-diabetic Korean women, mainly with respect to saturated fat intake.	Serum NGAL levels positively correlated with saturated fat intake. Serum NGAL levels were highest in the metabolic syndrome-risk group consuming higher saturated fat and lowest in the Super-healthy group consuming lower saturated fat.

Therapeutic effect of hybrid training of voluntary and electrical muscle contractions in middle age obese women with nonalcoholic fatty liver disease: a pilot trial.	Oh <i>et al.</i> (2015)	To assess the therapeutic efficacy of hybrid training (HYB) in people with nonalcoholic fatty liver disease (NAFLD).	NAFLD patients had attenuated intramyocellular lipid levels in the quadriceps after HYB. Levels of leptin, tumor necrosis factor- $\alpha$ , and interleukin-6 also reduced after HYB. HYB triggered a significant decrease in body weight, which was associated with a significant reduction in serum alanine aminotransferase, gamma-glutamyl transpeptidase, ferritin, oxidative stress levels, and insulin resistance values.
Effects of Hormone Therapy on Oxidative Stress in postmenopausal women with Metabolic Syndrome.	Sanchez-Rodríguez <i>et al.</i> (2016)	To determine the effect of oral hormone therapy (HT) on oxidative stress (OS) in postmenopausal women with metabolic syndrome (MetS).	MetS decreased in women who received HT (48%) after 6 months; triglycerides and high-density lipoprotein cholesterol improved.
High-protein intake during weight loss therapy eliminates the weight loss-induced improvement in insulin action in obese postmenopausal women.	Smith <i>et al.</i> (2016)	To investigate if the intake of different amounts of protein may influence on weight loss and insulin sensitivity.	Despite the weight loss and maintenance of lean tissue mass, a protein-rich diet seems not to have improved insulin signaling.
Inflammatory markers and cardiovascular risks among overweight-obese Emirati women.	Alkaabi <i>et al.</i> (2016)	To assess the correlations between inflammatory and oxidative biomarkers vs. anthropometric and metabolic measures, rates of dyslipidemia, diabetes, and hypertension and risks of cardiovascular disease.	There was positive correlation of interleukin 6 with waist circumference and adiponectin with HDL. Prevalence of triglycerides, dyslipidemia and hypertension was also greater among overweight/obese participants.
Reduction of serum advanced glycation end - products with a low calorie Mediterranean diet	Rodríguez <i>et al.</i> (2015)	To evaluate if low calorie Mediterranean diets would alter advanced glycation end-products (AGEs).	There was a significant decrease in mean body weight, body fat, waist circumference, total cholesterol, triglycerides and serum carboxymethyl-lisine; however, it was not feasible to correlate with the effects of the Mediterranean diet.
Increased expression of pro-inflammatory genes in abdominal subcutaneous fat in advanced chronic kidney disease patients	Witasp <i>et al.</i> (2011)	To quantify the subcutaneous adipose tissue (SAT) through biopsies and the serum/plasma concentrations of inflammatory markers and related protein products.	SAT had a significant upregulation of inflammatory pathway genes interleukin 6 and suppressor of cytokine signaling 3. There was also a down-regulation of leptin and the oxidative stress genes uncoupling protein 2 and cytochrome b-245, and alpha polypeptide comparing to controls.
Association of Oxidative Stress, Iron, and Centralized Fat Mass in Healthy Postmenopausal Women	Crist <i>et al.</i> (2009)	To determine the relationship between excess iron, oxidative stress, and centralized fat mass in healthy postmenopausal women.	Reduction in centralized fat mass and maintenance of a favorable lipid profile, antioxidant status, and iron status may be important to protect postmenopausal women from atherosclerotic cardiovascular disease.

There is evidence of a strong relationship between waist circumference and a greater IR, which may be associated due to the elevated circulation of free fatty acids in the bloodstream of people who are above their normal body weight (ALKAABI *et al.*, 2016).

Excessive body fat in older women may trigger a pro-inflammatory process in the adipose tissue, thus elevating the levels of tumor necrosis factor- $\alpha$ , and lipid and protein oxidation. Moreover, hereditary factors and eating habits may significantly influence the process of body weight gain.

An investigation conducted in non-diabetic Korean women evaluated the relationship of neutrophil gelatinase-associated lipocalin (NGAL) in episodes of disorders related to obesity (GY *et al.*, 2017). NGAL is also known as lipocalin-2 or growth factor-stimulated superinducible protein 24; it participates in a diversity of functions, including apoptosis and innate immunity, but chiefly in the response to bacterial infection. It is also expressed in tissues as kidney, liver, uterus and bone marrow and is thus a sensitive biomarker for various forms of kidney injuries. Gy *et al.* (2017) found that NGAL proportionally increased in those women with higher levels of obesity; it showed a positive correlation with body mass index (BMI), triglycerides, LDL- and total-cholesterol, interleukin-6, white blood cell count and neutrophils, and a negative correlation with HDL-cholesterol and superoxide dismutase activity. The study also revealed that the levels of NGAL were greatest in women who had a higher BMI consuming higher SFA and lowest in the eutrophic women consuming lower SFA.

A work developed in the University of Boston subjected 34 obese and sedentary postmenopausal women to diets with different contents of protein (SMITH, 2016). The aim was to determine whether the increased intake of this macronutrient as part of a balanced hypocaloric diet attenuated the weight loss-induced reduction in lean tissue mass, and the beneficial effect of losing 8%-10% of the initial body weight on the action of insulin. The sample was randomized to one of three interventions: 1) a weight loss (WL) group who received a hypocaloric diet containing 0.8 g protein/kg body weight daily; 2) a WL-high protein diet group who received a hypocaloric diet containing 1.2 g protein/kg body weight daily; and 3) a weight-maintenance control group. Sensitivity to insulin was assessed via the hyperinsulinemic-euglycemic clamp procedure in association with stable-isotope-labeled glucose tracer infusion and by evaluating muscle AKT phosphorylation. Regarding the inflammatory and OS defense markers, C-reactive protein and interleukin-6 concentrations in plasma, and muscle cluster of differentiation 68, interleukin-6, monocyte chemoattractant protein 1 and tumor necrosis factor- $\alpha$  gene expression were not altered during the interventions. Superoxide dismutase 1 gene expression, in turn, decreased after weight loss in those groups subjected to a hyperproteic diet. Thus, the work demonstrated that the intake of a high-protein diet during weight loss aids in reducing ROS and helps to preserve the lean tissue mass. Nevertheless, it interferes in the action of insulin on skeletal muscle, but the mechanisms through which it happens were not made clear by the study.

Rodríguez *et al.* (2015) tested the efficacy of a Mediterranean-type diet in reducing the advanced glycation end-products. A sample of 47 overweight and obese premenopausal women underwent a calorie restriction treatment during three months. They consumed 20 kcal/kg initial weight of a Mediterranean-type diet that excluded wine intake. Body composition, IR, lipoproteins and carboxymethyl-lisine (CML) serum levels were measured throughout the experimental period. Although the results were positive, since mean body weight, body fat, waist circumference, total cholesterol, triglycerides and serum CML had a significantly fall, the authors could not elucidate if the Mediterranean diet presents an additive effect to caloric restriction.

Another research carried out in 100 postmenopausal women with and without MetS assessed the effect of a 6-month oral hormonal therapy (HT) (1 mg/day of estradiol valerate plus 5 mg/10 days of medroxyprogesterone) on OS (SANCHÉZ-RODRIGUÉZ *et al.*, 2016). For that, four groups of 25 subjects were formed: 1) control, women without MetS receiving HT; 2) control, women without MetS taking placebo (pharmaceutical presentation similar to the treatment); 3) case, women with MetS receiving HT; and 4) case, women with MetS taking placebo. The participants were evaluated at baseline, 3 and 6 months. At the end of the experimental period, only 11 (48%) MetS women taking HT still had the diseases, while 20 (91%) MetS women receiving placebo continued with the disease. Moreover, two (9%) women without MetS taking HT and five (22%) women without MetS receiving placebo developed the disease. The study also verified that the concentration of lipid peroxides significantly reduced in both HT groups. The antioxidant components glutathione peroxidase (GPx) and antioxidant gap increased, and superoxide dismutase/GPx (SOD/GPx) ratio reduced in MetS women receiving HT. Women without MetS receiving HT only showed a significantly higher GPx compared with the baseline activity. No alterations were seen in the placebo groups. As for the OS score, the groups receiving HT showed a reduction along the study; the greatest effect was seen in MetS women, since a significant decrease was observed at 3 months. In women without MetS, the antioxidant effect was seen until month 6. The placebo groups presented a decreased OS score at month 3; nonetheless, it had increased in the final assessment.

Similarly, a randomized clinical trial was conducted with 122 postmenopausal women to determine the relationship among excess iron, OS and centralized fat mass (CRIST *et al.*, 2009). Results indicated a 4- to 7-fold range of catalase, SOD and GPx activity among the subjects. Furthermore, only 7.4% of women presented waist circumference values which were above the cutoff (88 cm). Therefore, most of them were not considered at high risk of chronic diseases. Median fasting insulin was within normal limits, but it varied nearly 10-fold; the glucose concentration, in turn, did not show a great alteration. As for the values of ferritin, hemoglobin, serum iron and transferrin saturation, no variations were observed. Crist *et al.* (2009) carried out a multiple regression analysis to assess the potential contributors to lipid peroxidation and centralized fat mass, and found a positive relationship between OS, serum iron levels, lipids, IR and centralized fat mass. There was a positive association between the iron status and the centralized fat mass, which possibly mediated the IR or the OS observed in the study population.

Witasp *et al.* (2011) evaluated 46 Swedish women through subcutaneous adipose tissue biopsies, serum/plasma concentrations of inflammatory markers and protein products. Thirty-seven of them had chronic kidney disease and 9 were nonuremic. The study tested the hypothesis that the uremic milieu in patients with chronic kidney disease may interact with the adipose tissue and thus trigger an unfavorable shift in its transcriptional output, even after correction for BMI. The research findings showed that the subcutaneous adipose tissue had a significant upregulation of inflammatory pathway

genes interleukin 6 (3.0-fold,  $P=0.0002$ ) and suppressor of cytokine signaling 3 (2.5-fold,  $P=0.01$ ), and a downregulation of leptin (2.0-fold,  $P=0.03$ ) and the OS genes uncoupling protein 2 (1.5-fold,  $P=0.03$ ) and cytochrome b-245, alpha polypeptide (1.5-fold,  $P = 0.005$ ) compared to controls.

In a pilot study, Oh *et al.* (2015) assessed the therapeutic efficacy of hybrid training (HYB) in cases of nonalcoholic fatty liver disease (NAFLD). HYB of voluntary and electrical muscle contractions was done to prevent disuse atrophy during space flight. The participants of the HYB program were 15 middle-aged obese women with NAFLD who had no improvement in serum alanine aminotransferase levels and/or liver fat deposition after 12 weeks of lifestyle counseling. Quadriceps and hamstrings HYB was performed for 20 min two times a week, and lasted 24 weeks. At the end of this period, patients had attenuated intramyocellular lipid levels in the quadriceps (-15.5%). Similar decreases were seen in levels of leptin (-17.4%), tumor necrosis factor- $\alpha$  (-23.2%) and interleukin-6 (-30.5%). The HYB intervention also promoted a significant body weight loss (-4.7%), which in turn was associated with a significant decrease in serum alanine aminotransferase (-35.8%), gamma-glutamyl transpeptidase (-21.6%), ferritin (-16.0%), OS levels (-17.8%) and IR values (-2.7%). Results allowed to conclude that HYB has an antiobesity effect and attenuates liver dysfunction and IR in association with an improvement in muscle strength and a decrease in ectopic muscle fat in NAFLD patients. Thus, HYB has great potential as a new type of exercise therapy for these subjects.

## CONCLUSION

This review aimed at searching for correlations between the occurrence of oxidative stress and insulin resistance in elderly women. Examination of the selected PubMed articles revealed that the high prevalence of abdominal adipose tissue in these women increases the risk of developing comorbidities as cardiovascular diseases and type II Diabetes Mellitus.

In this population, elevated circulating free fatty acid concentrations hamper signaling of the insulin receptors and raise the need for cellular lipid peroxidation, thus producing more metabolites from the reactions of the antioxidant system. Although other conditions, such as the reduction in hormone levels caused by menopause, can influence in the increase in reactive oxygen species, obesity is likely to be the major risk factor for the onset of insulin resistance and oxidative stress.

Reduction in body weight through the ingestion of calorie-restricted diets and participation in programs to increase physical activity seem to be good alternatives to lower the amount of abdominal adipose tissue, to strengthen the skeletal muscle, and to reduce oxidative stress and insulin resistance as well as other processes which are harmful to the health of the population.

Despite the evidence found in this assessment with regard to the elderly women population, further longitudinal studies are needed to improve elucidation of this correlation in geographically distinct populations.

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