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Oxidative Stress and Obesity: a Case-Control Study.

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DIDICATION

To my father Abdelkader, thank you for teaching me how to live intelligently and how to be honest, just and fair, thank you for your patience and understanding, Without your support and guidance I would not be where I am today.

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Heyet

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PREFACE

Obesity is a worldwide epidemic disorder that has become recognized in the 21st century as a principal health threat in most countries. Obesity is characterized by accumulation of excess body fat and is quantitatively defined as a body-mass index ≥ 30 kg/m^2. Several factors contribute to obesity and these can be broadly classified as genetic and environmental. Among the environmental influences, the combination of excess caloric intake and sedentary life contribute most significantly to the incidence of obesity. The American Obesity Association identifies obesity with more than 30 medical conditions. In particular, obesity is a risk factor for the development of common chronic diseases including hypertension, type 2 diabetes, metabolic syndrome, cardiovascular disease, several cancers, and a host of inflammatory disorders. On the other hand, in the past few decades there have been major advances in our understanding of the etiology of diseases and its causative mechanisms. Increasingly, it is becoming evident that free radicals are contributory agents, either to initiate or propagate the pathology or to add to an overall imbalance. The physiological production of the radical oxygen species is regulated by defense systems, when ROS generation overwhelms antioxidant capacity; the resulting accumulation of ROS has potent oxidative effects on many cellular constituents and leads to impairments of various cellular functions. Several data have reported that obesity may induce systemic oxidative stress and, in turn, oxidative stress is associated with an irregular production of adipokines, which contributes to the development of the metabolic syndrome.

The aim of this study is to summarize the relationship between oxidative stress and obesity, and if obese individuals have an over-expression of oxidative stress damages and pro-oxidants with under-production of antioxidant mechanisms, leading to the development of obesity-related complications.

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LIST OF ABBREVIATIONS

4-HNE	4-hydroxynonena
8-epi PGF2α	8-epi prostaglandin F2α
8-OHdG	8-hydroxydeoxyguanosine
ALT	Alanine transaminase
AST	Aspartate transaminase
ATP	Adenosine triphosphate
BMI	Body Mass Index
CAT	Catalase
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CNS	Central Nervous System
CRP	C-Reactive Protein
Cu	Copper
CVD	Cardiovascular Disease
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
Fe	Iron
FFA	Free Fatty Acids
FSH	Follicle-Stimulating Hormone
GLUT-4	Glucose Transporter Type 4
GPx	Glutathione Peroxidase
GR	Glutathione Reductase
GSH	Reduced Glutathione
GSSG	Oxidized Glutathione
HbA1c	Glycated Haemoglobin
HDL	High-Density Lipoproteins
HSE	Hospital Episodes Statistics
IL	Inter Leukine
LDL	Low-Density Lipoprotein
LPL	Lipoprotein Lipase
LPS	Lipopolysaccharides
LRC	Lipid Research Clinics
LV	Left Ventricular
MDA	Malondialdehyde
Mn	Manganese
mRNA	Messenger Ribonucleic Acid
NAD	Nicotinamide Adenine Dinucleotide
NADPH	Nicotinamide Adenine Dinucleotide Phosphat
NF-kB	Nuclear Factor-κB
NICE	National Institute for Health and Care Excellence

NOS	Nitric Oxide Synthase
NOX	NADPH Oxidase
OA	Osteoarthritis
PAI-1	Plasminogen Activator Inhibitor-1
PEROX	Paraoxonase
Q	Cardiac Output
RNS	Reactive Nitrogen Sepcies
ROH	Alcohol
ROOH	Hydroperoxides
ROS	Reactive Oxygen Species
Se	Selenium
SHBG	Sex-Hormone-Binding Globulin
SOD	Superoxide Dismutase
SV	Stroke Volume
TAC	Total Antioxidant Capacity
TBARS	Thiobarbituric Acid Reactive Substances
TG	Triglyceride
TNF-α	Tumor Necrosis Factor-α
UCP-1	Uncoupling Protein 1
VLDL	Very Low Density Lipoprotein
WC	Waist Circumferences
WHO	World Health Organization
WHR	Waist to Hip Ratio
XO	Xanthine Oxidase
ZAG	Zinc-α2-Glycoprotein
Zn	Zinc

CHAPTER I: REVIEW OF THE LITERATURE

1 Obesity

1.1 Definition of obesity:

Obesity is a worldwide epidemic disorder that has become recognized in the 21st century as a principal health threat in most countries [1]. Obesity is a complex condition, with serious social and psychological dimensions, affecting virtually all ages and socioeconomic groups [2]; it is also a disease [3].

Obesity is abnormal increase in the proportion of fat cells, mainly in the visceral and subcutaneous tissues of the body. Obesity may be exogenous or endogenous. Hyperplasic obesity is caused by an increase in the number of fat cells in the increased adipose tissue mass. Hypertrophic obesity results from an increase in the size of the fat cells in the increased adipose tissue mass.

Traditionally it has been defined as a weight at least 20% above the weight corresponding to the lowest death rate for individuals of a specific height, gender, and age (ideal weight). Twenty to forty percent over ideal weight is considered mildly obese; 40-100% over ideal weight is considered moderately obese; and 100% over ideal weight is considered severely, or morbidly, obese. The World Health Organization (WHO) and the National Institutes of Health define a person to be overweight when he or she has a BMI between 25.0 and 29.9 kg/m^2; and a person to be obese when he or she has a BMI $\geq$ 30.0 kg/m^2 [4]. The body mass index (BMI), calculated as weight in (kg) divided by height in (m) squared [5].

1.2 Epidemiology:

Obesity is considered the largest public health problem worldwide, especially in industrialized countries [6]. Obesity increases mortality and the prevalence of cardiovascular diseases, diabetes, and colon cancer [7]. Overweight and obesity are major risk factors for a number of chronic diseases. Once considered a problem only in high income countries, overweight and obesity are now dramatically on the rise in low- and middle-income countries, particularly in urban settings.

Changes in dietary and physical activity patterns are often the result of environmental and societal changes associated with development and lack of supportive policies in sectors such as health, agriculture, transport, urban planning, environment, food processing, distribution, marketing and education.

The current epidemic of obesity has been reported in several but not all regions globally. The highest rate of obesity has been reported in the Pacific Islands and the lowest rates have been seen in Asia. The rates in Europe and North American are generally high; while the rates in Africa and Middle Eastern countries are variable. The prevalence of obesity around the world

is monitored by the WHO through the global database on BMI [8]. The survey data included in the database are identified from the literature or from a wide network of collaborators.
In 2014, 39% of adults aged 18+ were overweight (BMI ≥ 25 kg/m^2) (39% of men and 40% of women) and 13% were obese (BMI ≥30 kg/m^2) (11% of men and 15% of women) [Figure I.1 and I.2]. Thus, nearly 2 billion adults worldwide are overweight and, of these, more than half a billion are obese [9].

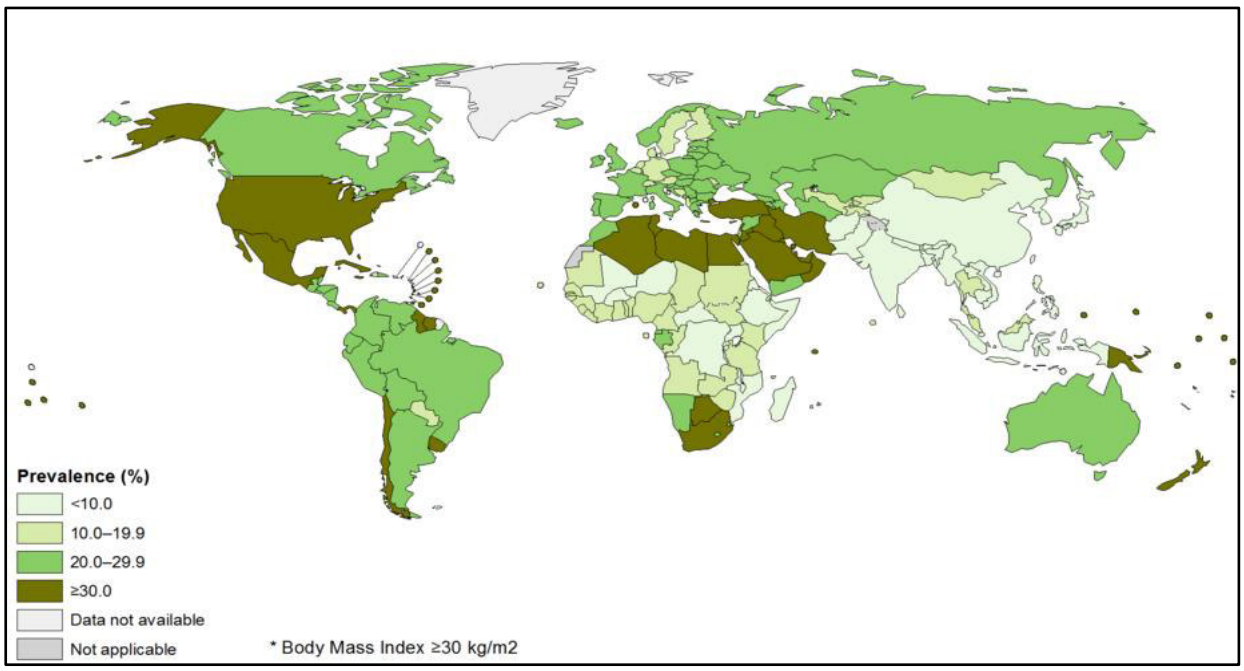


Figure I.1: World: Prevalence of obesity, ages 18+, age standardized: female, 2014 [9].

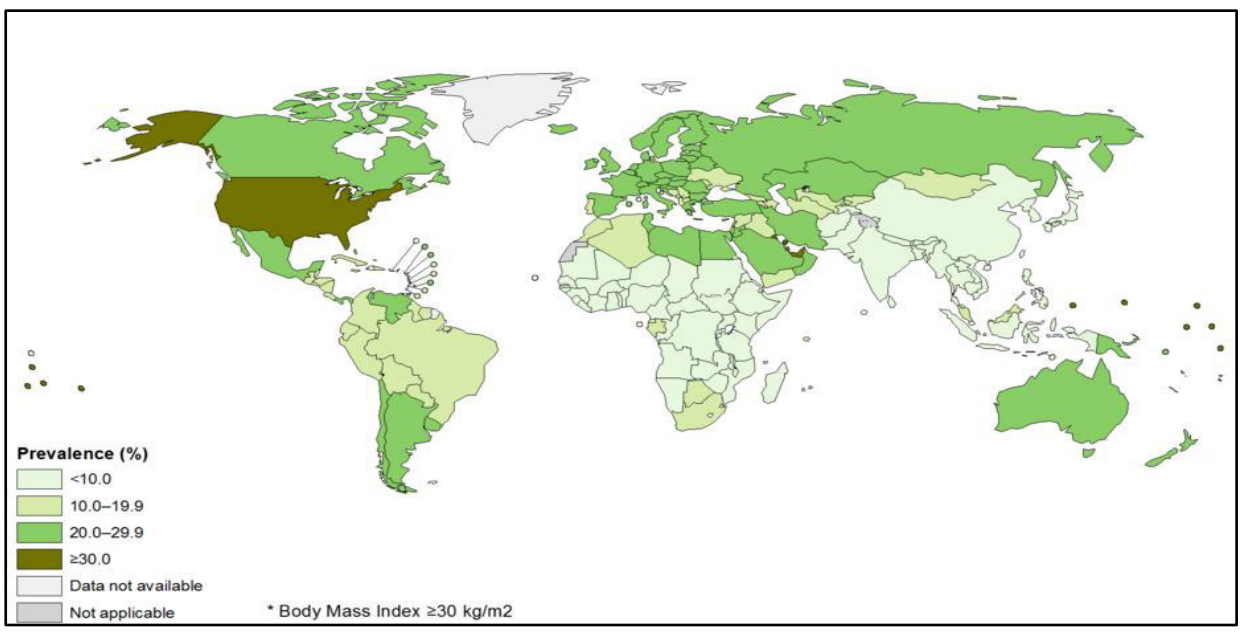


Figure 1.2: World: Prevalence of obesity, ages 18+, age standardized: male, 2014 [9].

❖ **Algeria:**

The project (TAHINA) in collaboration with National Institute Algerian public health in 2007 shows that among people aged between 35-70 years, 21.24 % were obese. The frequency is higher among women (14.12 %) than among men (8.76 %) [Figure 1.3] [10].

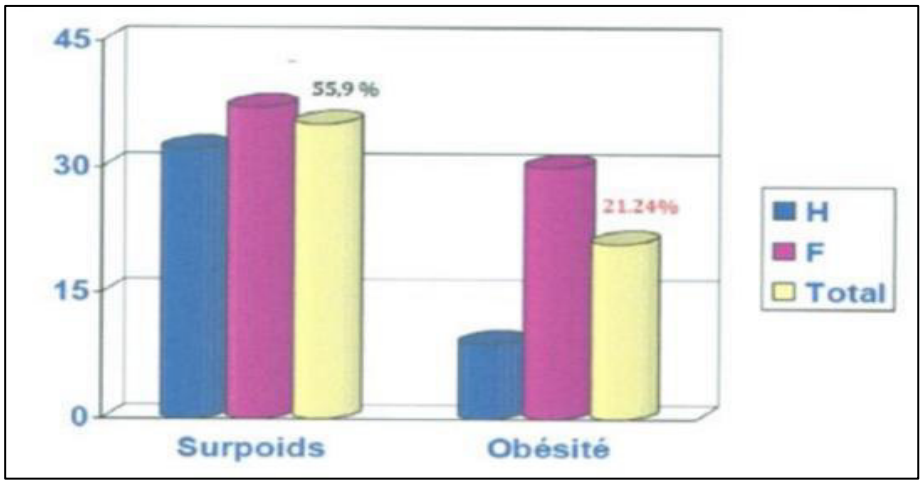


Figure I.3: The prevalence of obesity in Algeria [11].

- In 2010, the same project shows that the prevalence of obesity was 30.1 % in women and 9.1 % in men [11].
- In 2014, 18.9 % of men and 30.8 % of women aged 18+ were obese (BMI ≥30 kg/m^2) [12].

❖ **Tlemcen:**

An epidemiological survey was conducted from 2004 to 2005, among a representative sample of the city of Tlemcen. The prevalence of overall obesity is 19.2 %.

Women are more affected than men (27.9% against 10.5%). The prevalence of obesity and sex distribution reveals a significant difference between women and men [Figure1.4] [10].

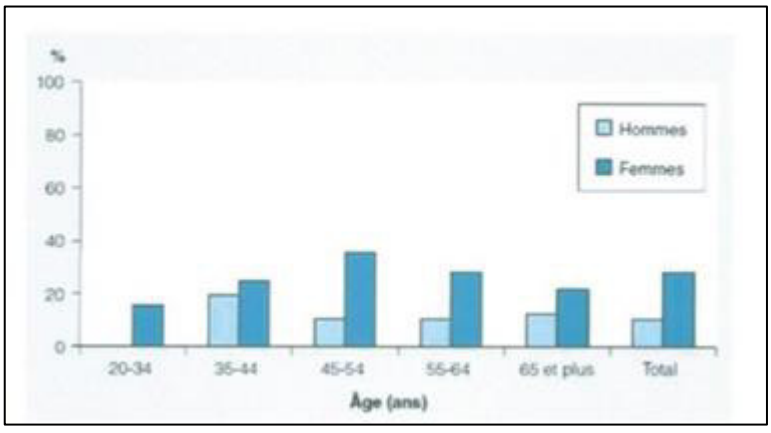


Figure 1.4: The prevalence of obesity by age and sex in Tlemcen [10].

There are various research reports and journal articles available that use HSE data to predict future obesity trends in adults.

HSE data from 1994 to 2004 were used as a basis of modelling obesity prevalence up to 2050. In 2007, the Foresight report estimated that:

- By 2025, 47 per cent of men and 36 per cent of women (aged between 21 and 60) will be obese.
- By 2050, it is estimated that 60 per cent of males and 50 per cent of females could be obese.

More recent modelling suggests that:

- By 2030, 41 per cent to 48 per cent of men and 35 per cent to 43 per cent of women could be obese if trends continue [13].

1.3 Measurement of overweight and obesity:

Body mass index (BMI), which is calculated as the weight in kilograms divided by the height in meters squared (kg/m^2), is the most widely used measure of obesity because of its low cost and simplicity.

BMI is the best way we have to measure the prevalence of obesity at the population level. No specialized equipment is needed and therefore it is easy to measure accurately and consistently across large populations. BMI is also widely used around the world which enables comparisons between countries, regions and population sub-groups. Height and weight data have been collected in each year of the HSE series, and waist circumference in most years. Height and weight data have been used to calculate BMI; waist circumference has been used to assess central obesity in adults.

In adults, a BMI of 25 kg/m^2 to 29.9 kg/m^2 means that person is considered to be overweight, and a BMI of 30 kg/m^2 or above means that person is considered to be obese.

The calculation of BMI is a widely accepted method used to define overweight and obese. Guidance published by the National Institute for Health and Clinical Excellence (NICE) states that within the management of overweight and obesity in adults, BMI should be used to classify the degree of obesity and to determine the health risks. However, this needs to be interpreted with caution as BMI is not a direct measure of obesity. BMI has limitations because it does not distinguish between lean mass and fat; it may overestimate body fat in well-trained body builders and underestimate body fat in older persons; moreover, BMI does not identify fat distribution.

It is now well recognized that abdominal fat is a major risk for obesity-related diseases: indeed, visceral fat accumulation contributes to pro-oxidant and pro-inflammatory states, as well as to alterations in glucose and lipid metabolisms. Waist circumference (WC) or waist-to-hip ratio (WHR) are useful indicators of visceral fat distribution.

NICE recommends the use of BMI in conjunction with waist circumference as the method of measuring overweight and obesity and determining health risks. Specifically, the guidance currently states that assessment of health risks associated with overweight and obesity should be based on both BMI and waist circumference for those with a BMI of less than 35 kg/m^2. Hence, the focus on using BMI combined with waist circumference in order to define overweight and obesity in adults [14].

Health is not only affected by how much body fat you have, but also by where most of the fat is located on your body. People who tend to gain weight mostly in their hips and buttocks have roughly a pear body shape, while people who tend to gain weight mostly in the abdomen have more of an apple body shape [15].

1.3.1 Measurement of Body Mass Index:

BMI is defined as weight in kilograms divided by the square of the height in meters (kg/m^2). BMI is an indicator of obesity; it is also used to classify obesity into class I, II and III [Table I.1].

Table 1.1: BMI ranges used to define BMI status [16].

Definition	BMI range (kg/m^2)
Underweight	Under 18.5
Normal	18.5 to less than 25
Overweight	25 to less than 30
Obese	30 to less than 40
Obese I	30 to less than 35
Obese II	35 to less than 40
Morbidly obese	40 and over
Overweight including obese	25 and over
Obese including morbidly obese	30 and over

1.3.2 Waist circumference:

Although BMI allows for differences in height, it does not distinguish between mass due to body fat and mass due to muscular physique, or for the distribution of fat. Therefore, waist circumference is also a widely recognized measure used to identify those with a health risk from being overweight. For men, low waist circumference in this classification is defined as less than 94 cm, high as 94–102 cm, and very high as greater than 102 cm. For women, low waist circumference is less than 80 cm, high is 80–88 cm and very high is greater than 88 cm [16].

1.3.3 Waist to Hip Ratio:

Waist to Hip Ratio (WHR) measurement can be used to help determine obesity. At the same time Waist to Hip Ratio helps indicate increased risk of disease and mortality. Ratios higher than 1.0 in men and 0.8 in women may indicate increased risk. Research has shown that people with a lot of fat stored in their tummy area ("apple" shaped people) are more likely to develop heart disease than those who store fat round their bottom and thighs ("pears") [17].

Thanks to WHR the distribution of fat is evaluated by dividing waist size by hip size. It is possible to have a high Body Mass Index (BMI) and a normal waist measurement if you are a fit, lean, muscular person. This is why your waist to hip ratio is a better guide to your risk of heart disease [18]. The higher the ratio the greater the risk of heart disease and strokes [19].

1.3.4 Relationships of BMI and WC to disease risk and mortality:

NICE guidelines on prevention, identification, assessment and management of overweight and obesity highlight their impact on risk factors for developing long-term health problems. It states that the risk of these health problems should be identified using both BMI and waist circumference for those with a BMI less than 35 kg/m^2. For adults with a BMI of 35 kg/m^2 or more, risks are assumed to be very high with any waist circumference [Table 1.2] [16].

Table I.2: NICE risk categories [14].

BMI Classification	Waist circumference		
	Low	High	Very high
Normal 18.5 to less than 25 kg/m^2	No increased risk	No increased risk	Increased risk
Overweight 25 to less than 30 kg/m^2	No increased risk	Increased risk	High risk
Obese I 30 to less than 35 kg/m^2	Increased risk	High risk	Very high risk
Obese II 35 to less than 40 kg/m^2	Very high risk	Very high risk	Very high risk
Morbidly obese 40 kg/m^2 and more	Very high risk	Very high risk	Very high risk

1.4 Etiology:

The imbalance increment of energy intake more than energy expenditure is considered the fundamental cause of obesity and overweight. Globally, there has been:

- The intake of high dense energy foods which involve fats, sugars and salt at the time they poor of essential micronutrients have been increased [20].
- Sedentary lifestyle because of forms of work, increased urbanization and changed modes of transportation which mean a little physical action.

When energy intake, as food eaten, exceeds energy output, as exercise or metabolic processes, the excess is stored as triglyceride in adipose tissue. Such an imbalance between intake and output may be due primarily to an increased food consumption or to a reduced energy expenditure, or both.

Heredity and environment each play a part in determining the imbalance which does not have to be large in absolute terms: a weight gain of 10 kg from age 25 to 55 requires only a 0.3% daily excess of intake over expenditure.

- Certain medical conditions: Cushing syndrome , depression, polycystic ovarian syndrome
- Certain medications (steroids, antidepressants)
- Genes, psychological makeup, and environmental factors all may contribute.

Genetic factors are believed to play a major role in such variation, according to twin, family and adoption studies. It has been calculated that up to 80% of the variance in body mass can be attributed to genetic factors. In the majority of cases, the hereditary influences are mediated through a number of genes (polygenic) each with a modest effect. Thus far, over 430 gene sites have been identified as possibly playing a part in the pathogenesis of obesity but the alarming rise in the prevalence of obesity, observed in the developed world in recent years, cannot plausibly be attributed to any change in genetic composition. It has all happened far too quickly for that. Thus, it must therefore be largely due to environmental factors which have affected both sides of the energy equation: food consumption having increased and energy expenditure decreased. The central nervous system, by means of signals, regulates appetite, energy intake, and weight gain; obesity can result from a failure of these signaling pathways [21]. A model showing the relationship of various factors associated with the control of body fat is illustrated in figure I.5.

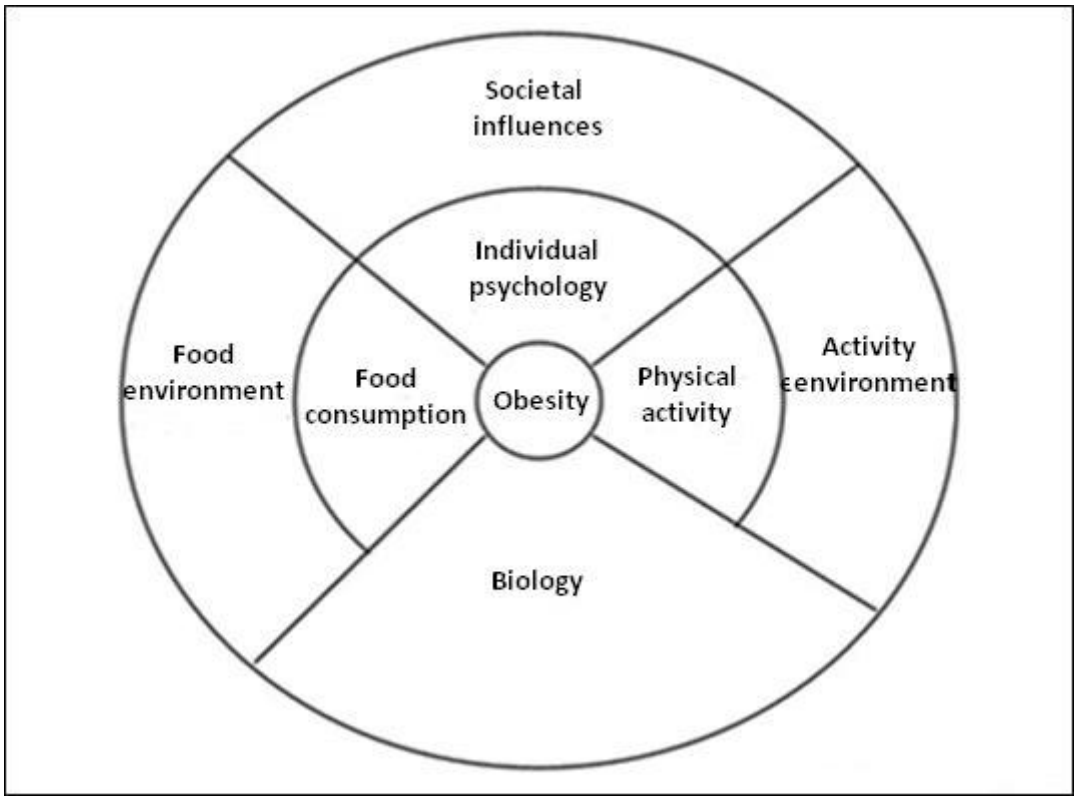


Figure I.5: A model showing the relationship of various factors associated with the control of body fat [20].

1.5 Pathophysiology:

1.5.1 Adipose tissue:

Human adipose tissue is divided into brown adipose tissue, which possesses multilocular adipocytes with abundant mitochondria that express high amounts of uncoupling protein 1 (UCP-1), which is responsible for the thermogenic activity of this tissue [22], and white adipose tissue, which is responsible for fat storage. Among the characteristics of white adipose tissue, we found that it consists of different cell types such as fibroblasts, preadipocytes, mature adipocytes, and macrophages. This tissue is very heterogeneous according to its visceral or subcutaneous location [23]. Adipocytes, the major constituent cell types of adipose tissues, possess the metabolic machinery to synthesize fatty acids (lipogenesis) and store them in the form of triglycerides during periods of abundant energy supply.

The fat cell is an endocrine cell, and part of an endocrine organ that is widely dispersed. The cell produces a variety of peptides and several metabolites [Figure I.6]. The pathological lesion in obesity is hypertrophy or enlargement of these fat cells. The enhanced secretion of peptides and metabolites from fat cells contributes to the pathophysiologic processes resulting from obesity [3].

The growing list of these signaling molecules, collectively termed adipokines, consists of several families of biologically active proteins including pro-inflammatory cytokines and cytokine-related proteins, complement and complement-related proteins, fibrinolytic proteins, proteins of the renin–angiotensin system, chemo-attractant proteins, growth factors and a variety of other biologically active proteins with hormone-like actions [24]. Adipokines such as leptin, TNF-α, IL-6, and chemerin have local autocrine and paracrine actions that regulate adipocyte metabolism, preadipocyte differentiation into adipocytes, and recruitment of immune cells (macrophages) and inflammation in white adipose tissue. Through endocrine actions, adipokines including leptin, adiponectin, resistin [25], TNF-α, and IL-6 have important roles in the regulation of inflammation and metabolic and vascular homeostasis. It is now widely accepted that the dysregulation of adipokine secretion in obesity is linked to the development of a chronic low-grade inflammation and insulin resistance that are central components of vascular and metabolic diseases [26].

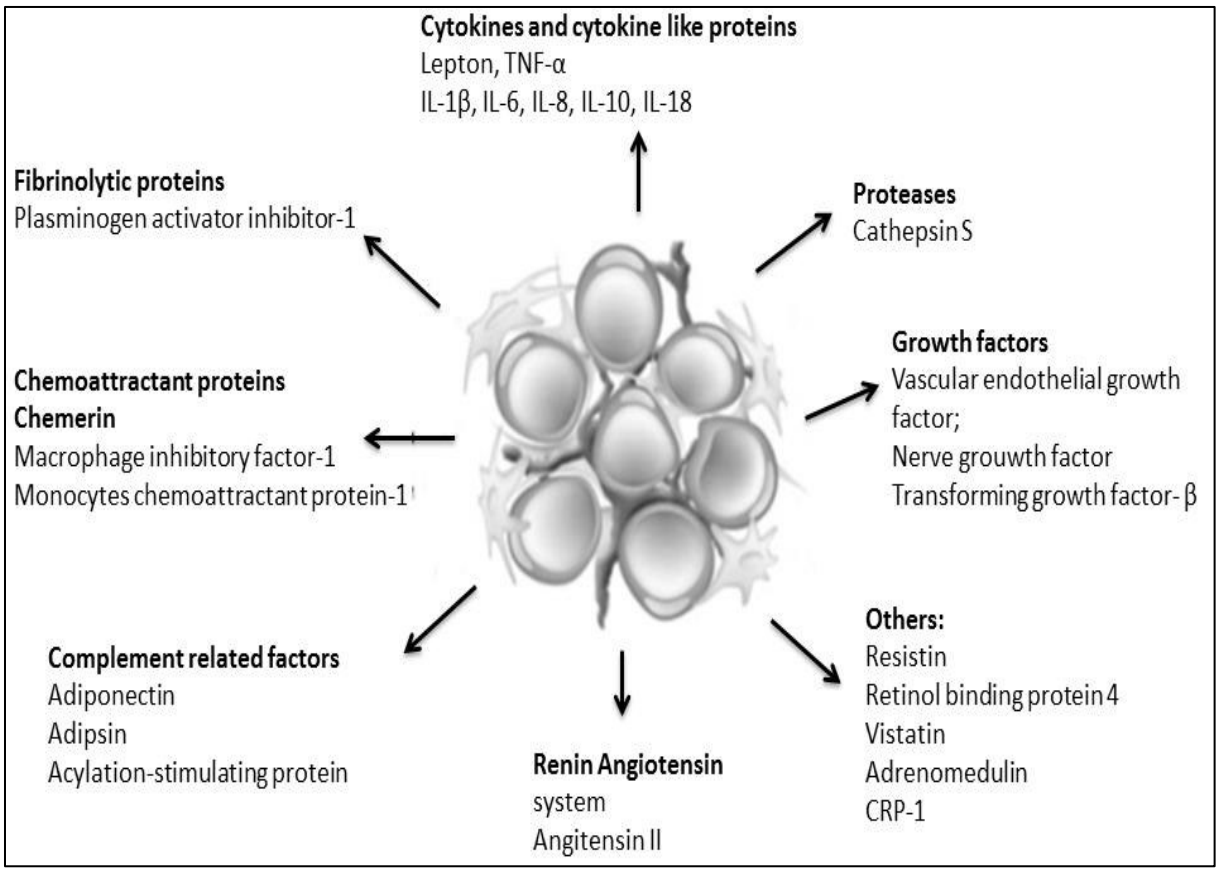


Figure I.6: Representative summary of adipose-derived signaling molecules [23].

1.5.2 Adipokines:

By strict definition, the "adipokine" term was devised in reference to cytokine molecules (adipocytokines) secreted by adipocytes. However, in recent years this term is more commonly used to cover a broad range of biologically active molecules secreted by white adipose tissue. Adipokines include pro-inflammatory cytokines and cytokine-related proteins, complement and complement-related proteins, fibrinolytic proteins, proteins of the renin–angiotensin system, and a variety of other biologically active proteins exerting hormone-like actions. In animals with obesity, there is a huge increase in white fat deposits due to the hyperplasia and hypertrophy of their adipocytes.

Hypertrophic-hyperplastic adipocytes exhibit a lower density of insulin receptors and a higher beta-3 adrenergic receptor, which facilitates the diapedesis of monocytes to visceral adipose stroma, initiating a pro-inflammatory cycle between adipo- and monocytes [27]. Adipose tissue is not only a triglyceride-storage tissue; studies in recent years have shown the role of white adipose tissue as a producer of certain substances with endocrine, paracrine, and autocrine action [28]. These bioactive substances are denominated adipokines or adipocytokines, among which are found plasminogen activator inhibitor-1 (PAI-1), tumor necrosis factor-alpha (TNF-α), resistin, leptin, and adiponectin [29]. These substances derive primarily from white adipose tissue and play a role in the homeostasis of various physiological processes [Figure I.7].

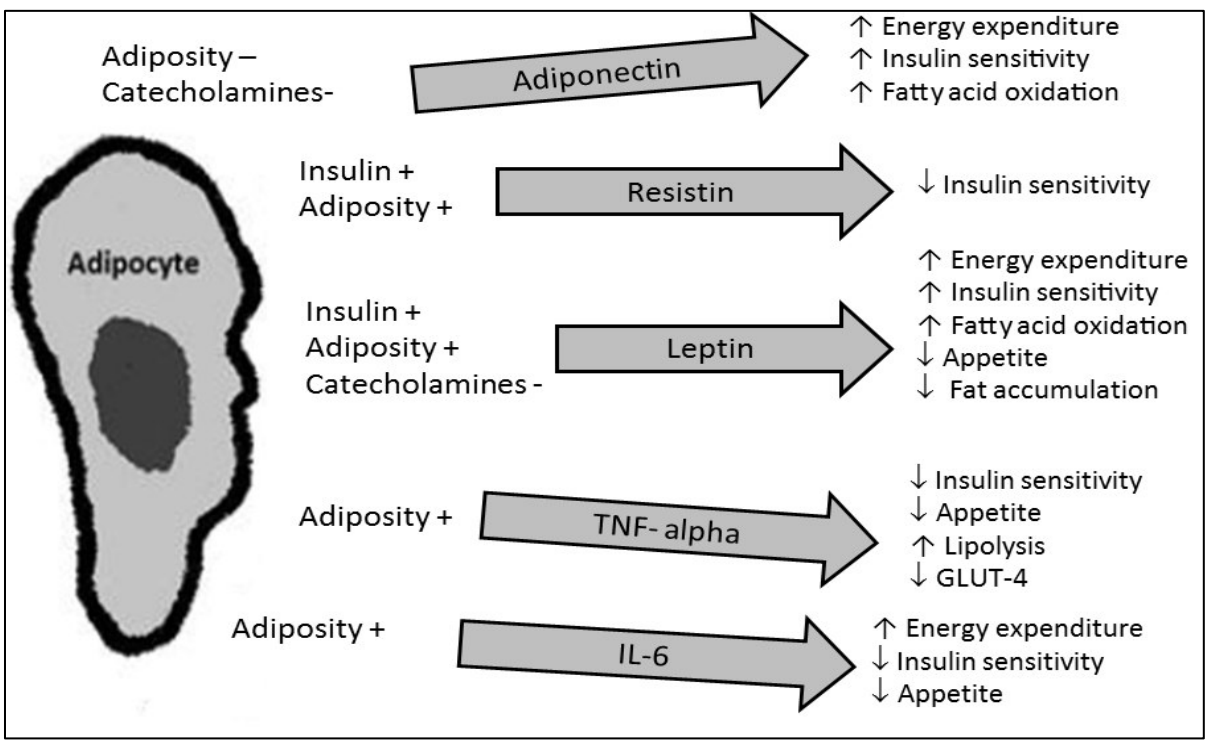


Figure 1.7: The major adipokines and their roles [24].

1.6 Consequences:

Obesity causes or exacerbates a large number of health problems, both independently and in association with other diseases. The greater the degree of obesity, particularly abdominal obesity, the greater the risk [30].

1.6.1 Cardiovascular disease, coronary heart disease, hypertension, and congestive heart failure :

Obesity is classified as a risk factor for cardiovascular disease (CVD) because of its effects on cardiac structure. In obese and overweight individuals, the cardiac structure and function changes as a result of an increase in total plasma and blood volume. These changes occur due to an increase in blood volume, which results in increased LV filling, an increase in stroke volume (SV), and finally an increase in absolute cardiac output (Q).

The effects of obesity and overweight affect cardiovascular disease from several different angles, including coronary heart disease (CHD) and atherosclerosis, and most predominantly, hypertension and congestive heart failure (CHF). Atherosclerosis develops through a progression from plaque formation to plaque rupture, formation of a thrombus, and then finally to fibrosis [31]. Obesity and distribution of body fat to the abdominal area have been linked to the promotion of plaque buildup and atherosclerosis. There are several other risk factors for CHD that are associated with obesity, including diabetes, insulin resistance, dyslipidemia, hypertension, LV hypertrophy, endothelial dysfunction, chronic inflammation, and obstructive sleep apnea [32].

1.6.2 Sudden death:

Autopsy results of obese sudden death patients show that ventricular hypertrophy is the most common finding. The three-generation Framingham Heart Study has shown that the sudden death is predictive for overweight and obese men and women based on the degree of overweight. This factor predicts independently of other CHD risk factors. The Framingham Heart Study also showed that obese individuals with CHF have a fivefold increased risk of sudden death compared to the general population [31].

1.6.3 Diabetes:

Approximately 85% of diabetics fall into the type 2 category and of these 70% are overweight, with a BMI of 30 or greater. It has been reported that the prevalence for type II diabetes is approximately 5 times higher for men and 8.3 times higher for women in obese groups compared to normal weight individuals. Furthermore, a gain in weight of 7.0-10.9 kg after the age of 18 years leads to a twice the risk for developing diabetes. The rate of type 2

diabetes has also risen in adolescents with physicians reporting one-third to one-half of new diabetic cases being type 2. The diabetes epidemic is on the rise on a worldwide level especially in non-European countries. Along with a genetic disposition, sedentary lifestyle, poor nutrition, and obesity are attributed to this problem. It has been demonstrated that obesity, especially central obesity, is associated with diabetes [33].

1.6.4 Arthritis:

Obesity is an important risk factor for osteoarthritis and gout. These health conditions are an important area to research due to the significant morbidity and cost to the community. Musculoskeletal conditions are the cause of a larger percentage of acute and chronic disability, the most common cause of work disability. There has been a consistent relationship between osteoarthritis and obesity. Obesity is a potential modifiable risk factor for this very expensive problem. There are several possible mechanisms that explain the association between obesity and osteoarthritis. Some of these include increased joint load and indirect metabolic changes. Other metabolic conditions that may be involved with the development of osteoarthritis include: hypertension, abnormal cholesterol and blood glucose levels, and uric acid [32]. Recent research suggests a link between these disorders and osteoarthritis, but the data are inconclusive at this time [34]. The adjusted risk of knee osteoarthritis was increased fourfold in men with a current BMI 23 to < 25 kg/m^2 as compared to men with BMI < 23 kg/m^2. BMI at 30 years of age was similarly related to knee osteoarthritis. These researchers concluded that a moderate increase in BMI, within the normal weight range, was significantly related to knee osteoarthritis among men. Being overweight at any time was related to knee osteoarthritis [35].

1.6.5 Pregnancy and infertility:

Obesity can affect fertility due to hormonal alterations that include: increased levels of gonadatropins and androgens which may cause anovulation, reduction in sex-hormone-binding globulin (SHBG), and increasing biologically active free androgens which are associated with anovulation. In relation to infertility, a recent study concluded that infertile women with an abnormal body mass and FSH levels significantly decrease the chance of pregnancy. Infertile women are advised that their chances of assisted reproduction treatment would increase with weight loss [36].

1.6.6 The psychological consequences of obesity:

Obese individuals are discriminated. Although more related to health care than mortality, psychological disorders affected by obesity include depression, anxiety, stress, bipolar disorder, schizophrenia, sleep apnea, sex disorders, weight stigma, dementia and other mental conditions, possibly even ending in suicide [36].

1.6.7 Other:

Other conditions associated with obesity include respiratory difficulties (a large waist circumference has been shown to be the strongest predictor for impaired lung function), asthma, gallbladder disease, chronic muscular-skeletal problems caused by stress on joints, osteoarthritis, heat injuries and heat disorders, skin problems and complications from hospital stays. Waist size of middle-aged females has also been found to be related to an increase in the rate of strokes [37].

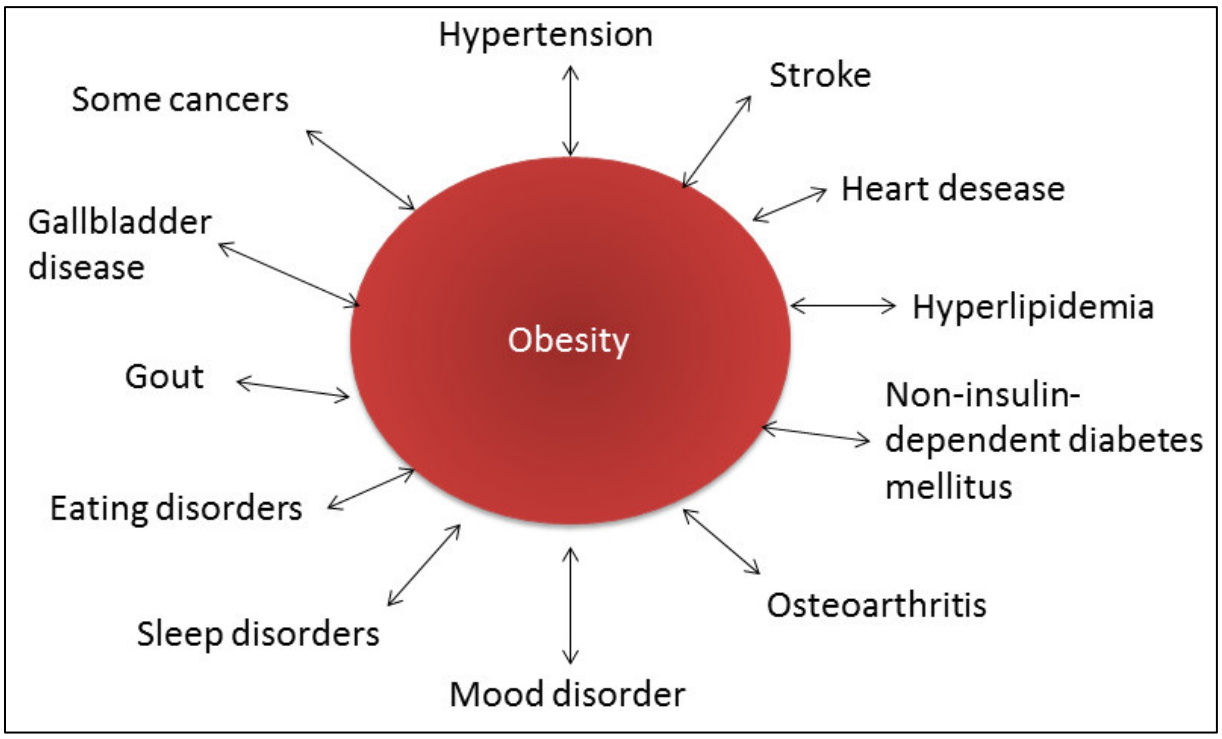


Figure I.8: Conditions associated with obesity.

The relationship of obesity to a variety of risks is shown figure I.8. Some of these risk factors can be related directly to the mass of extra fat (joint disease, sleep apnea, psychological responses) whereas others reflect metabolic consequences of an enlarged fat organ (diabetes, hypertension, heart disease, gallbladder disease and some forms of cancer) [3].

1.7 Management of obesity:

- For patients with a BMI of greater than 25 kg/m^2, obesity management starts with lifestyle modification through diet and physical activity.
- The management of obesity for patients with a BMI of between 30 and 40 kg/m^2, includes pharmacotherapy.
- For patients with severe obesity such as those with a BMI greater than 40 kg/m^2, surgery is recommended [Figure I.9] [Table I.3] [37].

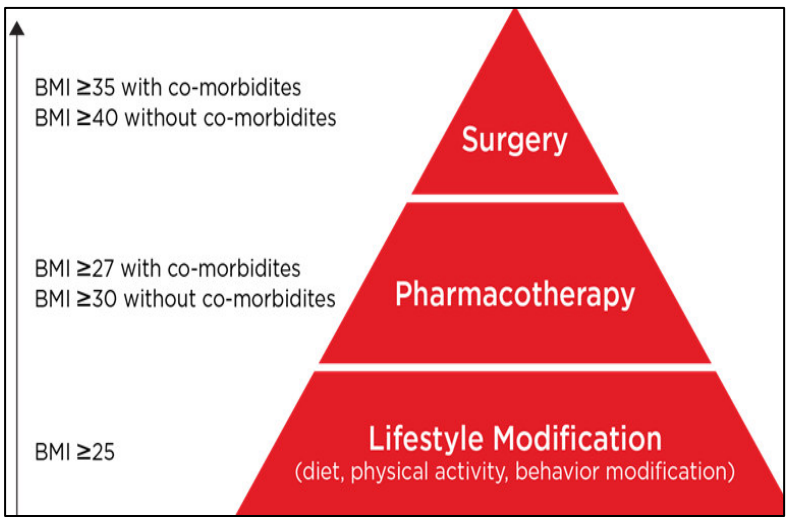


Figure I.9: Management of obesity.

Table 1.3: Management strategy to achieve weight loss [38].

BMI (kg/m^2)	**Risk**	**Nutrition**	**Physical Activity**	**Behavioral Management**	**Medications**	**Surgery**
25-29.9 Overweight	Low	X	X	X	*X+	Δ
30-34.9 Obese class I	Moderate	X	X	X	X	Δ
35-39.9 Obese class II	High	X	X	X	X	*X
>40 Obese class III	Severe	X	X	X	X	X
*May be considered if concomitant obesity –related risk factors or diabetes are present						
+May be initiated starting at a BMI of 27 or greater with comorbid disease						
Δ for obesity with related comorbidities						

2. Oxidative stress :

2.1 Introduction to oxidative stress:

Oxidative stress is a major mechanism in the initiation and progression of a wide variety of pathologies, including cardiovascular disease, type II diabetes, atherogenesis, chronic inflammatory processes, various neurodegenerative diseases and cancer, all of which are associated with the aging process [39].

Sies [40] has defined oxidative stress as "a disturbance in the prooxidant-antioxidant balance in favor of the former" [Figure I.10]. Thus oxidative stress is essentially an imbalance between the production of various reactive species and the ability of the organism's natural protective mechanisms to cope with these reactive compounds and prevent adverse effects [41].

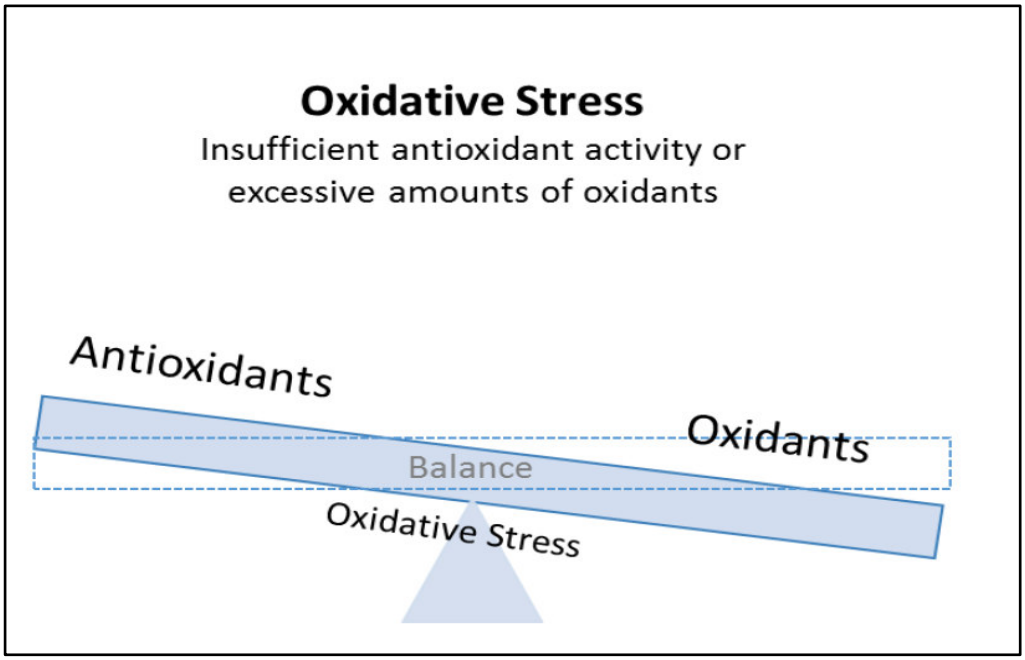


Figure I.10. Oxidants and antioxidants under normal conditions (balance) and during oxidative stress (disrupted balance due to insufficient antioxidant activity or excessive oxidants levels).

A critical point of oxidative stress is the formation of free radicals, overwhelming the antioxidant defense systems of the cells and interacting with different macromolecules, which include carbohydrates, proteins, phospholipids and nucleic acids, that become structurally modified by the process of oxidation. This is not only a consequence but also the cause of tissue homeostatic disturbances and represents a plausible mechanism underlying the pathophysiology of a wide number of metabolic diseases [42].

2.2 Free radicals:

A free radical is defined as any species that contains one or more unpaired electron [43]. Free radicals are also produced during normal metabolism and involved in enzymatic reactions, mitochondrial electron transport, signal transduction, activation of nuclear transcription factors, gene expression and the antimicrobial action of neutrophils and macrophages. Both reactive oxygen species (ROS) and reactive nitrogen species (RNS) have well- recognized beneficial and deleterious effects depending upon the concentrations. Under the normal physiological conditions, these molecules are produced at low/moderate concentrations and have a positive role [44]. Levels of free radicals depend on the pathophysiological and physiological state of the organism; for example, under physiological conditions, there is a homeostatic balance between the production of ROS and their elimination by antioxidants [45]. Alternatively, the overwhelming production of these molecules or failure of their combating strategies leads to oxidative stress-mediated damage to lipids, proteins, and DNA culminating in pathological conditions and aging [44].

2.2.1 Reactive oxygen species:

ROS is a broad term for various oxygen radicals and non-radical derivatives of O_2; they belong to the group of free radicals [Table I.4] [38]. In biological context the most important oxygen free radicals are superoxide and hydroxyl radical [46]. These radicals are very unstable and persist only for micro- or nanoseconds, but they trigger chain reactions and pass reactivity on to other, possibly more dangerous compound. The most common non-radicals are hydrogen peroxide, hypochlorous acid and singlet oxygen. They show higher stability, from minutes to hours and can therefore cause oxidative damage to biomolecules [47].

2.2.2 Reactive nitrogen species:

RNS are nitrogen-containing free radicals which possess high oxidizing potential and thus are involved in the oxidative stress. They are often classified as part of ROS, but the term RONS (reactive oxygen and nitrogen species) has also been used in the literature. The toxic effects of these molecules are often referred as “nitrosative stress” [48]. They mainly cause nitrosylation of the proteins, leading to alterations in their structure and function. The major RNS include nitric oxide and nitrogen dioxide [Table I.4], as well as non-radicals such as peroxynitrite besides others [49].

Similar to the highly reactive hydroxyl radicals, they are highly reactive and have a short half-life in aqueous environment. Since it is also a soluble lipid, it can diffuse through membranes and thus is critically important in neuronal signaling [50, 51].

Table I.4: List of the reactive oxygen and nitrogen species [52].

Type	Radicals	Non-radicals
ROS	Superoxide ($\cdot O_2^-$) Hydroxyl ($\cdot OH$) Peroxyl ($RO_2\cdot$) Alkoxyl ($RO^{-}\cdot$) Hydroperoxyl ($HO_2\cdot$)	Hydrogen peroxide (H_2O_2) Hypochlorus acid ($HOCL^-$) Ozone: (O_3) Singlet oxygen: $^1(O_2)$
RNS	Nitric oxide ($NO\cdot$) Nitrogen dioxide ($NO_2\cdot$)	Alkylperoxynitrites (ROONO) Nitrosyl cation (NO^+) Nitrosyl anion (NO^-) Dinitrogen tetroxide (N_2O_4) Dinitrogen trioxide (N_2O_3) Nitryl chloride (NO_2Cl) Peroxynitrite: $ONOO^-$ Nitrous acid: HNO_2

2.3 Sources of oxidative stress:

ROS and RNS are formed as by-products during physiological processes in cells and may depend on factors related to the lifestyle. Varied sources of free radicals have been discovered which can essentially be classified into exogenous and endogenous [Figure I.11] [53].

There are different cellular sources of ROS, including the mitochondrial electron transport chain, cellular oxidases and cytochrome P450 [52].

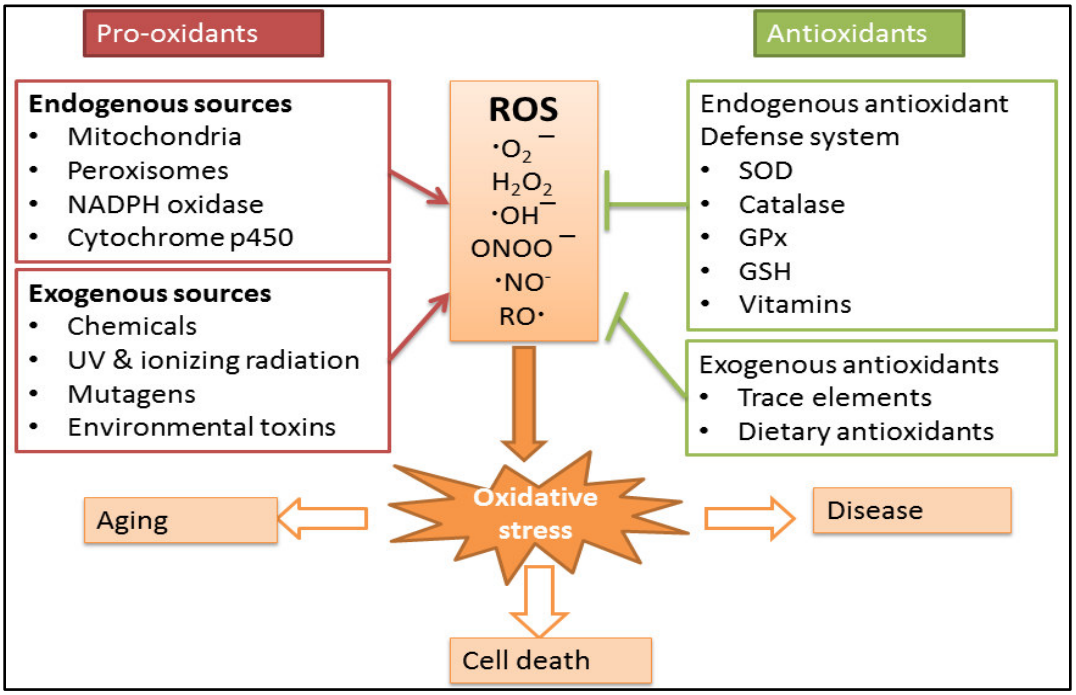


Figure I.11: Disturbance in the prooxidant-antioxidant balance leading to oxidative stress.

2.3.1 Mitochondria :

It is believed that under physiological conditions the mitochondrial respiratory chain is the most efficient source of ROS in a mammalian cell. In particular, defective mitochondria release large amounts of ROS. The ROS released by mitochondria can be scavenged by cellular antioxidant systems or, through HO-formation, cause oxidative damage to polyunsaturated fatty acids in the biomembranes, proteins, enzymes and nucleic acids [54].

Mechanistically, the ROS production occurs during the physiological process of ATP generation respiratory chain. During this process, the molecular ground-state oxygen can be activated to form singlet oxygen ($^1O_2$), by means of energy transfer, or by electron transfer, forming the superoxide anion radical ($\cdot O_2^-$) [Figure I.12] [44]. The major sources of radical generation within the mitochondria have been identified to be the NADH dehydrogenase and ubiquinone. Other sources of ROS in the mitochondria are the dehydrogenases, quinone oxidoreductase and monoamine oxidase B [55].

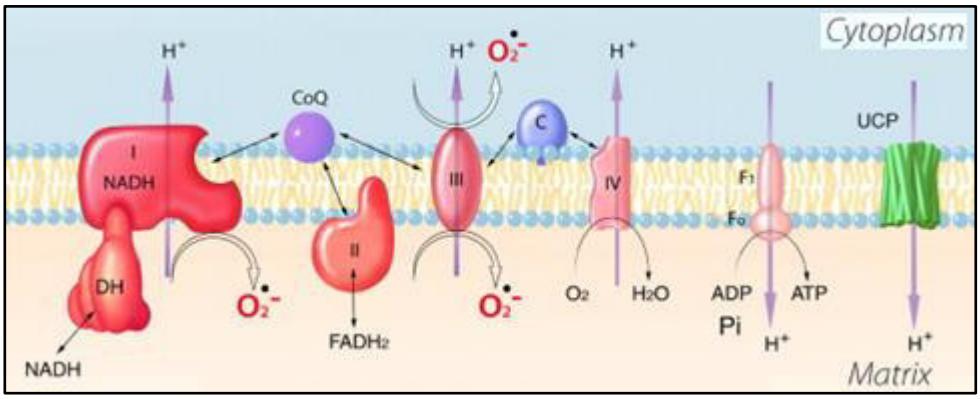


Figure I.12: Schematic model of ROS generation in the mitochondria [56].

2.3.2 Cellular oxidases:

Although mitochondrial respiratory chain is the major source of superoxide radicals, these molecular species can also be generated by one-electron reduction of oxygen by several different oxidases under certain conditions [57]. These oxidases include NADPH oxidase (NOX family) and xanthine oxidase. NOX enzymes are present in the lymphocytes, fibroblasts, endothelial cells, myocytes, and chondrocytes, where moderate amounts of ROS are produced and serve as a regulator of cell responses [58]. In response to infections or microbial invasion, the NOX family of enzymes is activated followed by a respiratory burst. These series of events lead to the increased oxygen consumption, glucose utilization, and increased production of reduced NADPH by the pentose phosphate pathway [59].

NADPH thus formed serves as an electron donor to an activated NADPH oxidase enzymatic complex in the plasma membrane to produce superoxide radicals from the oxygen molecule [50]. XO a cytosolic, nonheme enzyme is another prominent source of $\cdot O_2^-$ and H_2O_2 especially during the hypoxic conditions. Xanthine oxidase is a xanthine oxidoreductase, which exists primarily in the dehydrogenase form under normal physiological conditions. However, during hypoxia, xanthine oxidoreductase is converted to an oxidase form that can produce $\cdot O_2^-$ and hydrogen peroxide (H_2O_2) by using O_2 as an electron acceptor [60].

2.3.3 Nitric oxide synthases:

The enzyme nitric oxide synthase (NOS) produces NO$\cdot$ from O_2 and L-arginine, in the presence of NADPH, calcium, and/or biopterin as cofactors [61].

Under certain circumstances, NOS can produce $\cdot O_2^-$ together with NO$\cdot$, increasing the risk of in situ generation of $ONOO^-$ [57].

2.3.4 Cytochrome P450:

CYP is one of the most important classes of enzymes responsible for the oxidation of organic substances using lipids and steroids, as well as xenobiotics, as substrates. The catalytic action of CYP mirrors that of NOS enzymes where the formation of oxo-ferryl (FeIV = O), is the oxidizing form of the heme. Like in NOS, non-reduction of $Fe(III)O_2^-$ results in the production of $\cdot O_2^-$ [43].

2.3.5 Metal-catalyzed reactions:

H_2O_2 can be detoxified to H_2O and O_2 by the glutathione peroxidase (GPx) (in the mitochondria in conjunction with glutathione reductase) and catalase in peroxisomes, or it can act as a precursor for the more reactive species such as highly reactive hydroxyl radical [62]. HO$\cdot$ formed during this reaction is the strongest oxidizing agent known and reacts with organic molecules at diffusion-limited rates [50]. The superoxide and hydrogen peroxide will form the destructive hydroxyl radical and initiate the oxidation of organic substrates by Haber–Weiss reaction [44].

$$\cdot O_2^- + H_2O_2 \rightarrow HO\cdot + OH^- + O_2$$

However, this reaction of creating the hydroxyl radical requires a metallic catalyst (Cu^{2+} or Cu^{3+}) to proceed and is a combination of the transition metal mediated, chemical reactions called Fenton reaction [63].

$$Fe^{3+} + \cdot O_2^- \rightarrow Fe^{2+} + O_2$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + HO\cdot$$

The bioavailability of ferrous ions is the rate-limiting step in this reaction, but the recycling of iron from the ferric to the ferrous form by a reducing agent such as superoxide ions can maintain an ongoing Fenton reaction, leading to the generation of hydroxyl radicals. In the presence of trace amounts of iron, the other transition metals may also participate in these electron transfer reactions by cycling between oxidized and reduced states [44].

2.3.6 Other sources:

In addition to the above-mentioned noteworthy ROS and RNS sources, a plethora of other "radical" enzymes present in many cell types and tissues contribute toward the oxidative stress. These include mixed-function oxidases of the endoplasmal reticulum, the cytosolic enzymes such as lipoxygenases or cyclooxygenases, the peroxisomal enzymes (glycolate oxidase, D-amino acid oxidase, urate oxidase, fatty acyl Co-A oxidase), and even DNA methylating enzymes and enzymes involved in the synthesis of hormones and neurotransmitters [43].

2.4 Antioxidants:

Antioxidants can be described as substances that can, at relatively low concentrations, delay, prevent or remove oxidative damage to target molecule [39]. Humans have evolved highly complex antioxidant systems (enzymatic and non-enzymatic), which work synergistically, and in combination with each other to protect the cells and organ systems of the body against free radical damage. The antioxidants can be endogenous or obtained exogenously as a part of a diet or as dietary supplements. Some dietary compounds that do not neutralize free radicals, but enhance endogenous activity may also be classified as antioxidants [64].

An ideal antioxidant should be readily absorbed and quench free radicals, and chelate redox metals at physiologically relevant levels. It should also work in both aqueous and/or membrane domains and effect gene expression in a positive way. Endogenous antioxidants play a crucial role in maintaining optimal cellular functions and thus systemic health and well-being. However, under conditions, which promote oxidative stress, endogenous antioxidants may not be sufficient and dietary antioxidants may be required to maintain optimal cellular functions. The most efficient enzymatic antioxidants involve glutathione peroxidase, catalase and superoxide dismutase [65]. Non-enzymatic antioxidants include vitamin E and C, thiol antioxidants, metallothionein, carotenoids, natural flavonoids, and other compounds [66, 67]. There is growing evidence to support a link between increased levels of ROS and disturbed activities of enzymatic and non-enzymatic antioxidants in diseases associated with aging [64].

2.4.1 Enzymatic antioxidants

2.4.1.1 Superoxide dismutase:

This is one of the most effective intracellular enzymatic antioxidants and it catalyzes the conversion of superoxide anions to dioxygen and hydrogen peroxide [Figure I.13]. Superoxide dismutase exists in several isoforms, which differ in the nature of active metal center, amino acid composition, co-factors and other features. There are three forms of SOD present in humans: cytosolic CuZn-SOD, mitochondrial Mn-SOD, and extracellular-SOD [68].

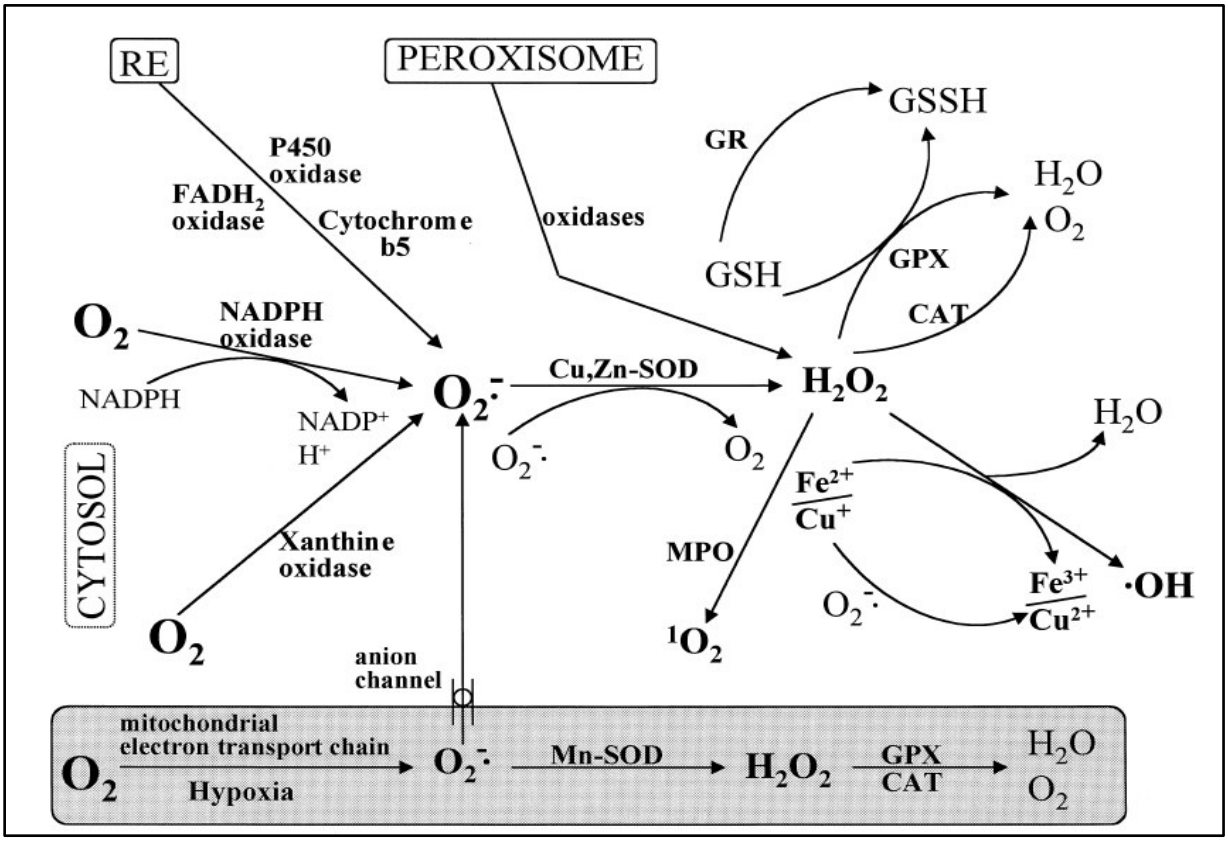


Figure I.13: Generation of ROS and the defense mechanisms of antioxidants.

2.4.1.2 Glutathione peroxidase:

Glutathione peroxidase refers to a family of multiple isozymes; it plays a critical role in the reduction of lipid and hydrogen peroxides [69]. In mammalian tissues, there are six GPx isozymes, namely, GPx1, 2, 3, 4, 5 and 6 [70]. GPx1, 2, 3 and 4 are selenoproteins. All of the GPx isozymes are able to catalyze the reduction of H_2O_2 or organic hydroperoxides (ROOH) to water or corresponding alcohols (ROH) using GSH as an electron donor [Figure I.14]. During the reactions, GSH is oxidized to glutathione disulfide (GSSG) [Figure I.15].

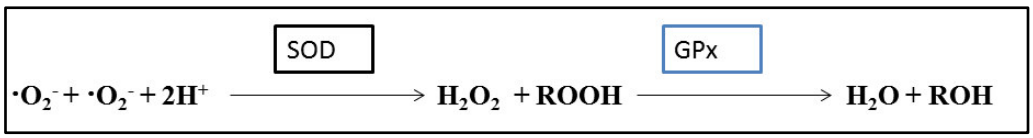


Figure I.14: Glutathione peroxidase reduces hydrogen peroxide and lipid peroxides to water and lipid alcohols [69].

2.4.1.3 Glutathione reductase:

As noted above, GSH, upon reaction with ROS, is oxidized to GSSG [Figure I.14]. In mammalian cells, the ratios of intracellular GSH to GSSG are high, usually in the range of 10:1 to 100:1. Maintenance of such high ratios of intracellular GSH to GSSG is essential for normal cellular activities, including redox signaling. Glutathione reductase (GR) reduces GSSG to GSH by using NADPH as a cofactor [Figure I.15] and is critical for maintaining the high ratios of intracellular GSH to GSSG [71].

By maintaining the high ratios of GSH to GSSG, GR plays an important role in detoxification of ROS as well as in the regulation of cellular redox homeostasis. GR-deficient mice are shown to be more susceptible to ROS-induced tissue injury [72]. Increased expression of GR in macrophages also decreases atherosclerotic lesion formation and vascular oxidative stress in low-density lipoprotein receptor-deficient mice [73].

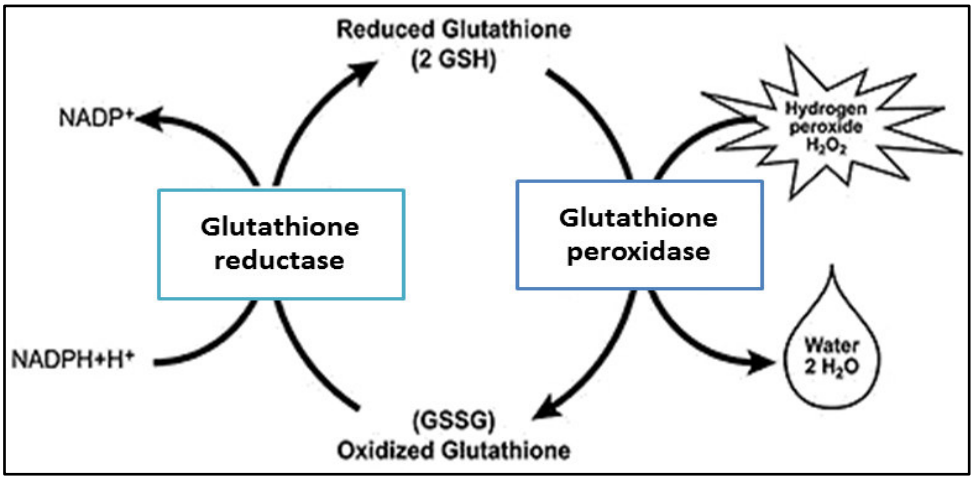


Figure I.15: Glutathione reduction oxidation cycle [73].

2.4.1.4 Catalase:

Catalase is an enzyme present in the cells of plants, animals and aerobic (oxygen requiring) bacteria. Catalase is located in a cell organelle called the peroxisome. The enzyme very efficiently promotes the conversion of hydrogen peroxide to water and molecular oxygen [44].

2.4.2 Non-enzymatic antioxidants:

2.4.2.1 Vitamin E:

This is a fat-soluble vitamin existing in eight different forms. In humans, α-tocopherol is the most active form, and is the major powerful membrane bound antioxidant employed by the cell [74]. The main function of vitamin E is to protect against lipid peroxidation [75], and there is also evidence to suggest that α-tocopherol and ascorbic acid function together in a cyclic-type of process. During the antioxidant reaction, α-tocopherol is converted to an α-tocopherol radical by the donation of a labile hydrogen to a lipid or lipid peroxyl radical, and the α-tocopherol radical can therefore be reduced to the original α-tocopherol form by ascorbic acid [76].

2.4.2.2 Vitamin C:

Vitamin C (ascorbic acid) is the most important vitamin in fruits and vegetables. Except human and other primates, most of the phylogenetically higher animals can synthesize vitamin C (L-ascorbate). More than 90% of the vitamin C in human diets is supplied by fruits and vegetables. Vitamin C is defined as the generic term for all compounds exhibiting the biological activity of L-ascorbic acid. Ascorbic acid is the principal biologically active form but L-dehydroascorbic acid, an oxidation product, also exhibits biological activity. Vitamin C is required for the prevention of scurvy and maintenance of healthy skin, gums and blood vessels. It functions in collagen formation, absorption of inorganic iron, reduction of plasma cholesterol level, inhibition of nitrosoamine formation, enhancement of the immune system, and reaction with singlet oxygen and other free radicals [77]. Vitamin C is an important and powerful water-soluble antioxidant and thus works in aqueous environments of the body; it is an electron donor and therefore a reducing agent [78]. Its primary antioxidant partners are vitamin E and the carotenoids as well as working along with the antioxidant enzymes. As mentioned above, vitamin C cooperates with vitamin E to regenerate α-tocopherol from α-tocopherol radicals in membranes and lipoproteins [74], and also raises intracellular glutathione levels thus playing an important role in protein thiol group protection against oxidation [79]. Ascorbic acid also inhibits lipid peroxidation, oxidation of low-density lipoproteins and protein oxidation [80]; it can react directly with superoxide, hydroxyl radicals and singlet oxygen [81].

2.4.2.3 Thiol antioxidants:

The major thiol antioxidant is the tripeptide glutathione (GSH), which is a multifunctional intracellular antioxidant and is considered to be the major thiol-disulphide redox buffer of the cell. It is abundant in cytosol, nuclei, and mitochondria, and is the major soluble antioxidant in these cell compartments [82].

2.4.2.4 Co-factors:

The biochemical definition of a co-factor is that it is an ion or a molecule that binds to the catalytic site of an apoenzyme rendering it active. Many enzymes have a requirement for metal ions for their activity and these metal ions are also referred to as co-factors. The major antioxidant enzymes possess transition metals or selenium at the catalytic site and the availability of cofactors can determine the activity of such enzymes [64].

Different essential metals play an important role in controlling oxidative reactions in biological tissues. For example copper (Cu) is an essential cofactor in a number of critical enzymes including cytochrome C oxidase and copper, zinc-superoxide dismutase (CuZn-SOD) [83]. Although unregulated Cu is also a well-known pro-oxidant it can through the action of transporter proteins such as metallothionein and ceruplasmin exert its antioxidative effects. A Cu deficiency-induced decrease in the activity of CuZn-SOD in humans and animals has been reported [84]. Copper deficiency also decreases the activity of ceruloplasmin, which requires Cu for its ferroxidase function [85], and it can also lead to a reduction in enzymes of the oxidant defense system such as selenium-dependent glutathione peroxidase (Se-GPx) and catalase. Furthermore a deficiency in Cu can also alter other ROS scavengers including metallothionein and the non-protein thiol, glutathione [86].

Iron (Fe) is an essential constituent of catalase enzymes, hemoglobin and myoglobin, but is also a prooxidant (via Fenton reactions) when it is present in excess [87]. Thus, iron chelators such as albumin, haptoglobin, lactoferrin, transferrin and urate also have an important role to play in preventing oxidative stress-related diseases [64].

Selenium (Se) is another important co-factor and epidemiological findings have linked a lowered Se status to neurodegenerative and cardiovascular diseases as well as to an increased risk of cancer [88]. There is an association between Se reduction and DNA damage, and oxidative stress [89].

The element manganese (Mn) is another co-factor involved in antioxidant defense mechanisms and is a vital component of Mn-SOD enzyme, which plays a crucial role in protecting mitochondria from free radical attack [64].

Zinc (Zn) another component of SOD is also involved in antioxidant defense systems and protects the vascular and immunological systems from the damaging effects of free radical species [90]. Evidence supports the fact that Zn deficiency can impair the host protective mechanisms designed to protect against DNA damage [91], and it also plays an important role as an antioxidant and/or as a co-factor in keeping the skin healthy, thus it can play an important role in healthy aging [92].

2.4.2.5 Other antioxidants:

In addition of the antioxidants mentioned above, there are others which play an important role to prevent oxidative stress [Table I.5].

2.5 Food and oxidative stress:

Studies have revealed that increased consumption of grains, fruits and vegetables is associated with reduced risk of diseases. This may be attributed to the presence of natural antioxidants such as vitamin C, tocopherols, carotenoids, polyphenolics and flavonoids which prevent free radical damage. The plant phenolics are commonly present in fruits, vegetables, leaves, nuts, seeds, barks, roots, etc. The antioxidant property of phenolics is mainly due to their redox properties. They act as reducing agents, hydrogen donors, singlet oxygen quenchers and metal chelators [93].

Nutritional oxidative stress describes an imbalance between the prooxidant load and the antioxidant defense as a consequence of excess oxidative load or of inadequate supply of the organism with nutrients [94].

Postprandial oxidative stress is characterized by an increased susceptibility of the organism toward oxidative damage after consumption of a meal rich in lipids and/or carbohydrates [95]. Thus, macronutrients have an effect on the redox balance in the organism. They are either targets of oxidative modifications after absorption or are present in a prooxidant form in the diet. Hyperlipidemia and hyperglycemia have been associated with increased oxidative damage affecting lipoproteins and the antioxidant status [94].

Table I.5: Different antioxidants and their effects [71].

Antioxidants	Location/Sources	Remarks
Uric acid	Wide distribution	Uric acid is a powerful antioxidant and is a scavenger of singlet oxygen and radicals like superoxide anion, hydroxyl, and binds transition metals.
Cysteine	Wide distribution	Cysteine is also a vital component for the synthesis of glutathione and can reduce organic compounds by donating e^- from SH groups, N-acetyl-L-cysteine act as glutathione precursor and scavenges of H_2O_2 and peroxide.
Co-enzyme Q10	Synthesized in human cells	It inhibits lipid peroxidation, reduces mitochondrial oxidative stress, and also able to recycle vitamin E.
Transferrin	It is a major iron transporting protein in the body	It binds free iron salts, which can leads to the generation of ROS.
Lactoferrin	It is a milk protein found extracellularly	Similar action like transferring to helps in iron binding.
Ceruloplasmin	A metal binging protein in extracellularly	It is a copper binding protein. It catalyses the oxidation of Fe^{2+} to Fe^{3+} while oxygen is reduced to water.
Bilirubin	Blood stream tissue, plasma and extravascular place	It is an end product of heme catabolism, generally viewed as cytotoxic, lipid-soluble waste product. But at micromolar concentrations in vitro, efficiently scavenges peroxyl radicals and protects albumin-bound linoleic acid from peroxyl radical-induced oxidation.

2.6 Concept of oxidative stress and molecular damage:

ROS can damage various cellular components, such as proteins, lipids, and DNA. They can damage mitochondrial macromolecules either at or near the site of their formation. Oxidative stress causes different diseases via four critical steps; membrane lipid peroxidation, protein oxidation, DNA damage and disturbance in reducing equivalents of the cell; which leads to cell destruction, altered signaling pathways [Figure I.16] [96].

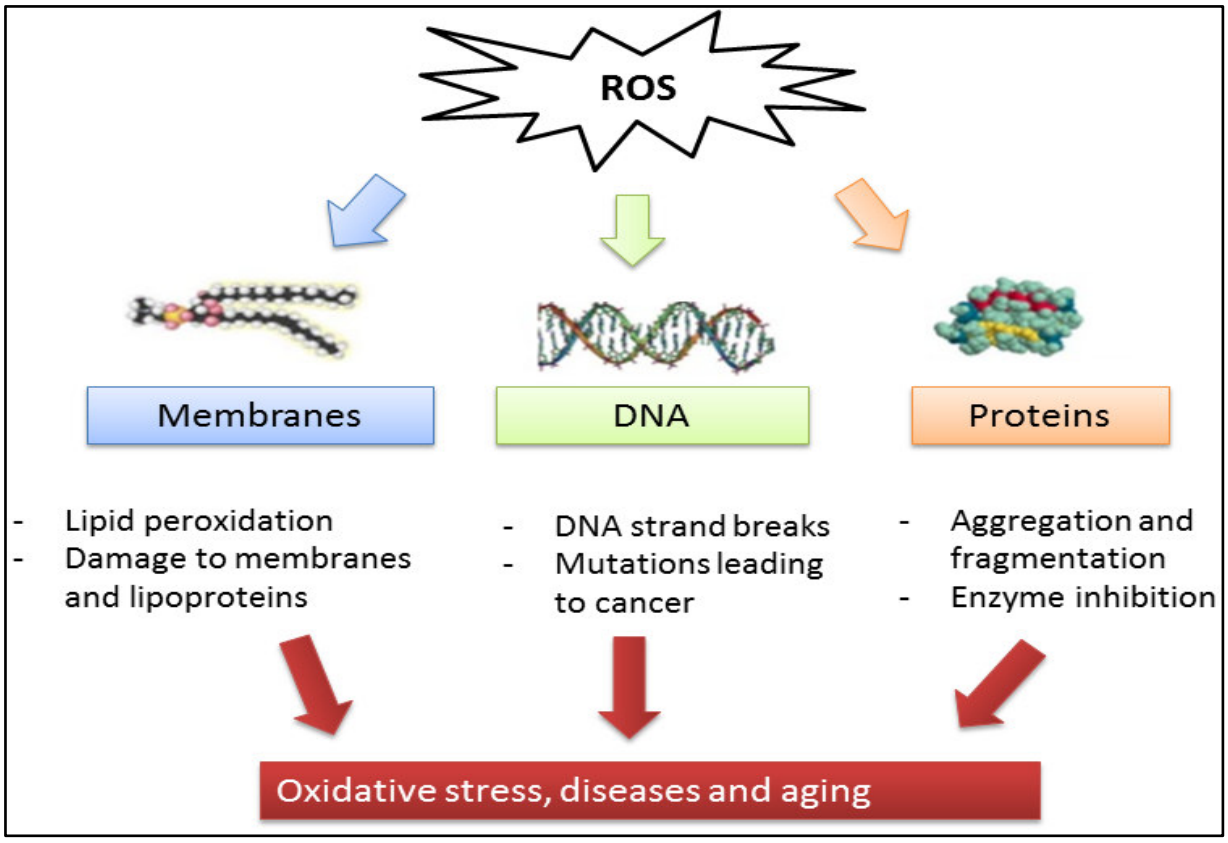


Figure I.16: Molecular damage of ROS

2.6.1 Lipids:

Lipids present in membrane of subcellular organelles are highly susceptible to free radical damage. Free radical when reacted with lipid can undergo the highly damaging chain reaction of lipid peroxidation leading to both direct and indirect effects. Lipid peroxidation leads the generation of large number of toxic by-products that can have effects at a site away from the area of generation, act as 'second messengers' [97]. Lipid peroxidation induced damage is highly detrimental to the functioning of the cell. Lipid peroxidation in cell membranes can damage cell membranes by disrupting fluidity and permeability. Peroxidation of lipid is initiated by the attack of a species, which can remove a hydrogen atom from a methylene group, resulting the formation of an unpaired electron on the carbon atom (·CH). Carbon radical thus formed is stabilized by molecular rearrangement to produce a conjugated diene, which then can react with an oxygen molecule to form a lipid peroxyl radical (ROO·). These radicals can react with other lipid molecules to abstract hydrogen atoms further, so that lipid hydroperoxides (ROOH) forms and at the same time propagate other lipid peroxidation further [98].

2.6.2 Proteins:

Proteins are also susceptible by the free radicals directly. Free radicals can cause the damage of many kind of protein, interfering with enzyme activity and function of structural protein. A highly reactive and stable product such as protein hydroperoxides can generate by the oxidation of proteins caused by ROS/RNS, which can generate additional radicals mainly upon interaction with transition metal ions. Although most oxidized proteins are functionally inactive in nature and are rapidly removed, but some can gradually accumulate with time and thereby contribute to the damage associated with ageing as well as various diseases [99].

2.6.3 DNA:

ROS/RNS interfere with DNA and lead to oxidative damage. DNA is highly susceptible to damage by the free radicals such as ·OH. Theses can react with DNA by addition or loss of hydrogen atoms from the sugar moiety. In particular, the C4-C5 double bond of pyrimidine is very sensitive to attack by ·OH, which results generation of a spectrum of oxidative pyrimidine damage products, such as thymine glycol, uracil glycol, urea residue, 5-hydroxydeoxyuridine, 5-hydroxydeoxycytidine, hydantoin and others [74]. Likewise, purines are susceptible to attach by ·OH which leads to the generation of 8-hydroxydeoxyguanosine (8-OHdG), 8-hydroxydeoxyadenosine, form amidopyrimidines and other less characterized purine oxidative products. Free radical attack also causes the activation of the poly (ADP-ribose) synthetase enzyme which can leads to fragmentation of DNA and programmed cell death. This process depletes the cellular level of NAD^+ levels thereby disrupting electron transport chain function [99].

2.7 Biomarkers of oxidative stress:

Evaluation of the oxidative stress holds great significance and has been a major challenge due to lack of sensitive and robust methods to accurately measure the levels of ROS and cellular defense systems [100].

In humans, redox balance is generally evaluated by measuring markers of antioxidant defense and/or oxidative stress. Plasma concentrations of molecules (vitamin E, vitamin C, glutathione, uric acid), minerals (especially selenium and zinc), as well as antioxidant enzyme activities are the most widely used biomarkers of the antioxidant state [Table I.6].

Another useful biomarker is the total antioxidant capacity (TAC) that evaluates the integrated action of all antioxidants present in plasma [101].

Table I.6: Biomarkers of oxidative stress

Antioxidants	
Vitamin C	Vitamin C is consumed in the presence of oxidative stress [102].
GSH/GSSG	During oxidative stress, GSH is usually consumed. It is thus important to measure the level of oxidized GSH (GSSG) and to calculate the GSH/GSSG ratio in order to get a more precise idea of the level of oxidative stress [103].
SOD	Low SOD levels may reflect low levels of oligoelements, but there is no absolute correlation between the former and the latter. In the presence of oxidative stress, SOD shows two different behaviors. First, in response to a moderate level of oxidative stress, the organism overexpresses SOD. Then, if the stress persists and involves massive production of toxic ROS, SOD is destroyed and its concentration drops. Paradoxically, a too-high SOD concentration can be dangerous, because it leads to overproduction of hydrogen peroxide (paradoxical effect of antioxidants) [68].
GPx	Seleno-dependent glutathione peroxidase behaves in two different ways in the presence of oxidative stress: first the enzyme is overexpressed and then, if the oxidative stress persists, it is destroyed. A reduced GPx activity may reflect too little selenium in the diet [104].
TAC: Total antioxidant Capacity	This test consists in evaluating the capacity of whole blood or plasma to inhibit ROS production in an in vitro ROS-generating system. It is thus a screening method that sums the various individual activities of all the antioxidants present in a biological medium [105].
Coenzyme Q10	Like vitamin E, it can inhibit lipid peroxidation [106].
Uric acid	Uric acid increases during oxidative stress, principally during ischemia-reperfusion [107].

Oligoelements	
Selenium	This oligoelement is not itself an antioxidant, but it participates in defense against ROS as a co-factor of glutathione peroxidase [88].
Copper	Cu is one of the essential co-factors of SOD. Yet like iron and as a transition metal, Cu plays a major role in triggering reactions leading to ROS production. An excessive Cu concentration may thus reflect the presence of oxidative stress. Several studies have shown an increase in the serum level of copper during ageing [108].
Zinc	Zinc deficiency generally results in increased sensitivity to oxidative stress [109].
Cu/Zn ratio	Zn competes with Cu for uptake in the gut and is thought to serve as a natural antioxidant. In several cases, the Cu/Zn ratio proved to be a better predictor of disease severity and/or mortality than Cu levels [110].
Markers of oxydation	
LDL oxidation	Patients at high risk of stroke or heart attack (owing to hypertension, hypercholesterolaemia, obesity, kidney dialysis) have abnormally high oxidized LDL levels. Spectrophotometric measurement of oxidized LDL, based on determination of conjugated dienes, is less sensitive and less specific than the recently developed immunological methods [111].
8-OHdG	Guanine is readily transformed to 8-hydroxy-2'-deoxyguanosine (8-OH-dG), which is normally eliminated by DNA repair enzymes. When the body's DNA repair systems are deficient, 8-OH-dG accumulates in the DNA, causing mutations involved in cancer development. The 8-OH-dG concentration must be normalized with respect to creatinin when it is measured in urine [112].

3. Obesity and oxidative stress:

ROS occur under physiological conditions and in many diseases and cause direct or indirect damage in different organs; thus, it is known that oxidative stress is involved in pathological processes such as obesity, diabetes, cardiovascular disease, and atherogenic processes. It has been reported that obesity may induce systemic oxidative stress and, in turn, oxidative stress is associated with an irregular production of adipokines, which contributes to the development of the metabolic syndrome [113]. The sensitivity of CRP and other biomarkers of oxidative damage are higher in individuals with obesity and correlate directly with BMI and the percentage of body fat, LDL oxidation, and triglyceride levels [114]; in contrast, antioxidant defense markers are lower according to the amount of body fat and central obesity [115]. A research showed that a diet high in fat and carbohydrates induces a significant increase in oxidative stress and inflammation in persons with obesity [116].

3.1 Mechanisms of formation of free radicals during obesity:

There are several possible contributors to oxidative stress in obesity, including hyperglycemia, increased muscle activity to carry excessive weight, elevated tissue lipid levels, inadequate antioxidant defenses, chronic inflammation, endothelial ROS production, and hyperleptinemia. These factors are not mutually exclusive. Rather, obesity may involve some or all of these contributors to systemic oxidative stress. Depending on the status of the obese individual, one contributor may exert a greater oxidative stress effect than the others, but this contribution may change as the metabolic and physical status of the individual changes [117].

3.1.1 Adipose tissue:

The increase in obesity-associated oxidative stress is probably due to the presence of excessive adipose tissue itself, because adipocytes and preadipocytes have been identified as a source of proinflammatory cytokines, including TNF-α, IL-1, and IL-6; thus, obesity is considered a state of chronic inflammation. These cytokines are potent stimulators for the production of reactive oxygen and nitrogen by macrophages and monocytes; therefore, a rise in the concentration of cytokines could be responsible for increased oxidative stress. TNF-α also inhibits the activity of CRP, increasing the interaction of electrons with oxygen to generate superoxide anion [118]. Adipose tissue also has the secretory capacity of angiotensin II, which stimulates NADPH oxidase activity. NADPH oxidase comprises the major route for ROS production in adipocytes [119].

3.1.2 Fatty acid oxidation:

Mitochondrial and peroxisomal oxidation of fatty acids are capable of producing free radicals, therefore, oxidative stress, which could result in mitochondrial DNA alterations in the oxidative phosphorylation that occurs in mitochondria, causing structural abnormalities and depletion of ATP. However, it is also possible that mitochondrial abnormalities are preexisting conditions that allow for overproduction of ROS [120].

3.1.3 Overconsumption of oxygen:

Obesity increases the mechanical load and myocardial metabolism; therefore, oxygen consumption is increased. One negative consequence of increased oxygen consumption is the production of ROS as superoxide, hydroxyl radical, and hydrogen peroxide derived from the increase in mitochondrial respiration and, of course, from the loss of electrons produced in the electron transport chain, resulting in the formation of superoxide radical [121].

3.1.4 Accumulation of cellular damage:

Excessive fat accumulation can cause cellular damage due to pressure effect from fat cells (*i.e.,* non-alcoholic steatohepatitis). Cellular damage in turn leads to high production of cytokines such as TNF-α, which generates ROS in the tissues, increasing the lipid peroxidation rate [122].

3.1.5 Type of diet:

Another possible mechanism of ROS formation during obesity is through diet. Consumption of diets high in fat may alter oxygen metabolism. Fatty deposits are vulnerable to suffering oxidation reactions. If the production of these ROS exceeds the antioxidant capacity of the cell, oxidative stress resulting in lipid peroxidation could contribute to the development of atherosclerosis [121].

3.1.6 Role of mitochondria in the development of oxidative stress in obesity:

Mitochondria provide the energy required for nearly all cellular processes that ultimately permit the carrying out of physiological functions; additionally, they play a central role in cell death by the mechanism of apoptosis. Mitochondrial dysfunction has been implicated in a variety of diseases ranging from neurodegenerative diseases to diabetes and aging. Obesity takes place in disorders that affect mitochondrial metabolism, which favors ROS generation and the development of oxidative stress. On the other hand, another mechanism has been proposed that involves an effect of high triglyceride on the functioning of the mitochondrial

respiratory chain, in which intracellular triglyceride, which is also high, inhibits translocation of adenine nucleotides and promotes the generation of superoxide [122].

The mitochondrial process of oxidative phosphorylation is very efficient, but a small percentage of electrons may prematurely reduce oxygen, forming potentially toxic free radicals, impairing mitochondrial function. Beyond that, under certain conditions, protons can be reintroduced into the mitochondrial matrix through different uncoupling proteins, affecting the control of free radical production in mitochondria [123]. Uncoupling proteins possess an amino acid sequence that is utilized to identify potential mitochondrial carriers [124].

3.2 Obesity and antioxidant capacity:

When obesity persists for a long time, antioxidant sources can be depleted, decreasing the activity of enzymes such as SOD and CAT [7]. The activity of SOD and GPx in individuals with obesity is significantly lower compared with that in healthy persons, having implications for the development of obesity-related health problems [125]. A study in rats showed that the liver concentration of vitamin A having antioxidant activity was significantly lower in rats with obesity compared with those without obesity; the concentration of vitamin A in rats with obesity probably indicates the dilution of this fat-soluble vitamin in high liver lipid storage [126]. In addition to vitamin A, levels of serum antioxidants, such as vitamin E, vitamin C, and glutathione, are decreased in obesity [127]. In addition to this, ROS decrease the expression of adiponectin, suggesting that treatment with antioxidants or ROS inhibitors could restore the regulation of adipokines [128]. Thus, supplementation with antioxidants would reduce the risk of complications related with obesity and oxidative stress [129].

CHAPTER II: RESEARCH METHODOLOGY

I. Introduction :

Obesity is a social problem worldwide and a chronic disease of multifactorial origin that develops from the interaction of social, behavioral, psychological, metabolic, cellular, and molecular factors. It is the condition under which adipose tissue is increased and can be defined as an increase in body weight that results in excessive fat accumulation. The World Health Organization (WHO) defines obesity as a body mass index (BMI) ≥ 30 kg/m^2.

Obesity represents a major risk factor for a plethora of severe diseases, including diabetes, cardiovascular disease, non-alcoholic fatty liver disease, and cancer. It is often accompanied by an increased risk of mortality.

Growing evidence allows us to understand the critical role of adipose tissue in controlling the physio-pathological mechanisms of obesity and related diseases. Recently, adipose tissue, especially in the visceral compartment, has been considered not only as a simple energy depository tissue, but also as an active endocrine organ releasing a variety of biologically active molecules known as adipocytokines or adipokines. Based on the complex interplay between adipokines, obesity is also characterized by chronic low grade inflammation which leads to a permanently increased oxidative stress.

Oxidative stress is a general term for cellular damage caused by an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense in the body. Oxidative damage has also been implicated in the pathogenesis of many chronic progressive diseases, such as cancer, inflammation, and neurodegenerative disorders as well as vascular disease.

Oxidative stress may be the unifying mechanism underlying the development of comorbidities in obesity. Evidence suggests that a clustering of sources of oxidative stress exists in obesity: hyperglycemia, hyperleptinemia, increased tissue lipid levels, inadequate antioxidant defenses, increased rates of free radical formation, enzymatic sources within the endothelium and chronic inflammation.

To understand its role in the development of major obesity-related complications, it is important to investigate if obesity is associated with increased systemic oxidative stress.

The aim of this case-control study was to examine the association between oxidative stress and obesity by evaluating oxidative stress biomarkers.

2. Subjects and methods:

A case-control study was performed at the public Tlemcen University Hospital, between September, 2015 and March, 2016.

This study comprised 30 obese volunteers between the ages of 18 and 65 years and compared their data to 30 non-obese healthy control participants matched in age and gender. The participants were stratified into either the non-obese or obese group according to World Health Organization criteria using body mass index.

The nature, benefits, and risks of the study were explained to the volunteers who read and signed a written informed consent statement before participation and completed a health history questionnaire which is also a detailed questionnaire concerning dietary habits, socioeconomic variables and lifestyle for each subject.

All participants had to meet the following criteria before enrollment in the study:

- Having body mass index (BMI) ≥ 30 kg/m^2 for obese group;
- Having body mass index (BMI) <25 kg/m^2 for control group;
- No current or historical chronic health problems;
- No cardiovascular, metabolic, degenerative or respiratory disease;
- Non-smoking;
- Not being on a diet;
- No participation in regular physical activity;
- Not taking any herbal or antioxidant supplements; or receiving prescription medication.

2.1 Anthropometric measurements:

Height and weight were determined as well as waist circumference which was measured at the level of the umbilicus with the subjects standing and breathing normally. In this study, BMI was used as indicator of obesity. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Systolic and diastolic blood pressures were measured in each participant with a standard mercury sphygmomanometer on the right arm.

2.2 Blood samples:

Venous blood was collected from each individual between 08:30 and 10:30h after over-night fasting (>10 hours). 10 ml of venous blood was collected from each patient, 2 ml into heparin tube, 2 mL into an EDTA tube and 4 ml into two plain tubes.

The serum was separated and devised to be conserved at 4°C for vitamin C determination (with-in 24 hours) and kept frozen at -80°C for analysis of copper and zinc.

2.3 Analytical procedures:

2.3.1 Metabolic control :

Heparin bottle tubes were reserved for the determination of routine laboratory analyses: glucose, triglycerides, total cholesterol, ALT, AST, creatinine, urea, uric acid, calcium and phosphorus. All these assays were carried out on an automated chemistry analyzer (SIEMENS) and the tests from collected samples were carried out in the laboratory of the Department of Biochemistry.

Reagents used:

- Glucose Flex Reagent: (Siemens #DF40)
- Triglycerides Flex Reagent: (Siemens #DF69A)
- Total cholesterol Flex Reagent: (Siemens #DF27)
- ALT Flex Reagent: (Siemens #DF143)
- AST Flex Reagent: (Siemens #DF41A)
- Creatinine Flex Reagent: (Siemens #DF33A)
- Urea Flex Reagent: (Siemens #DF21)
- Uric acid Flex Reagent: (Siemens #DF77)
- Calcium Flex Reagent: (Siemens #DF23A)
- Phosphorus Flex Reagent: (Siemens #DF61)

The blood samples collected in the EDTA bottle tubes, were used to determinate the glycated hemoglobin (HbA1c).

HbA1c was measured using D-10™ HbA1c Program, ref: 220-0101

The D-10 HbA1c Program utilizes principles of ion-exchange high-performance liquid chromatography (HPLC).

2.3.2 Oxidative stress parameters:

Plain bottles tubes were used for the determination of the oxidative stress status parameters. The parameters used for assessing oxidative stress are zinc, copper and vitamin C.

Samples were centrifuged at 4000 rpm for 10 min, upper serum was obtained by pipette and put in separate Eppendorf tubes treated the same day for the determination of vitamin C concentration and stored in -80°C for until measurement of zinc and copper concentrations.

Copper and zinc were measured in 60 serum samples using the Randox colorimetric copper (Cu2340) and zinc (Zn2341) assays. Vitamin C was examined by colorimetric method.

2.3.2.1 Copper determination:

- **Principle of the method:**

At pH 4.7 copper, is released by a reducing agent. It then reacts with a specific color reagent, 3.5-Di-Br-PAESA 4-(3,5-Dibromo- 2-pyridylazo)-N-Ethyl-N-(3-sulphopropyl) aniline, to form a stable, colored chelate. The intensity of the color is directly proportional to the amount of copper in the sample.

- **Stability and preparation of reagents:**

R1a. Buffer Supplied ready for use. Stable up to expiry date when stored at +2 to +8 C.°
R2. Chromogen Supplied ready for use. Stable up to expiry date when stored at +2 to +8 C.°
R1b. Reagent Dissolve the contents of 1 vial of Reagent R1b with 20 ml of Buffer R1a. Ensure that contents are completely dissolved. Stable for 2 weeks at +2 to +8 C.°
Standard (CAL) Supplied ready for use. Stable up to expiry date when stored at +2 to +8 C.°

- **Procedure:**

Temperature:	37 C°
Wavelength	580 nm (570 - 590 nm)
Pathlength:	1 cm
Reaction:	Endpoint
Measurement:	Against Reagent Blank

Pipette into cuvette:	Reagent Blank	Standard	Sample
Double Distilled H_2O	60µl	-	-
Sample	-	-	60µl
Standard	-	60µl	-
Reagent 1	1000 µl	1000µl	1000µl
Mix and allow to stand for 60 seconds at 37 °C. Read initial absorbance (A1) of sample and standard against the reagent blank.			
Chromogen R2	250 µl	250µl	250µl
Mix, incubate for 5 minutes at + 37° C and read final absorbance (A2) against reagent blank.			

- **Manual calculation :**

Concentration = $\frac{\Delta A \text{ sample}}{\Delta A \text{ standard}} \times \text{conc.of standard}$

ΔA = A2 - A1

Normal value in serum:

- Male 11.0 – 24.0 µmol/l (70 - 150 µg/dl)
- Female 12.6 – 24.4 µmol/l (80 - 155 µg/dl)

2.3.2.2 Zinc determination:

- **Principle of the method:**

Zinc present in the sample is chelated by 5-Br-PAPS 2-(5-bromo-2-pyridylazo)-5-(N-propyl-N-sulfopropylamino) -phenol in the reagent. The formation of this complex is measured at a wavelength of 560 nm.

- **Preparation of solutions:**

All reagents are supplied ready to use. Stable up to expiry date when stored at +15 to +25°C.

R1. Deproteinizing Solution

R2a. Color Reagents A

R2b. Color Reagents B

CAL. Standard

❖ **Preparation of working reagent R2:**

Mix color reagents A(R2a) and B(R2b) in a 4:1 ratio, e.g. 20 ml A + 5 ml B. Stable for 2 days at +15 to +25 °C or 1 week at +2 to +8°C.

➢ **Procedure 1: deproteinization**

Pipette into test tube:			
	Blank H2O	Standard STD	Test Sample
Test Specimen	0.5(0.2) ml	0.5(0.2) ml	0.5(0.2) ml
Deproteinizing Reagent R1	0.5(0.2) ml	0.5(0.2) ml	0.5(0.2) ml
Mix, well then centrifuge for 10 mins at 10,000 g. Use supernatant in the zinc assay within 2 hours.			

➢ **Procedure 2: zinc assay**

Wavelength: 580 nm (570 - 590 nm)

Incubation Temperature: 20/25 °C

Pathlength: 1 cm light path

Pipette into test tube:			
	Blank H2O	Standard STD	Test Sample
Supernatant	0.5(0.2) ml	0.5(0.2) ml	0.5(0.2) ml
Working Reagent	2.5(1.0) ml	2.5(1.0) ml	2.5(1.0) ml
Mix, incubate for 5 min at 25°C. Measure the absorbance of the standard (A standard) and the sample (A sample) against the reagent blank within 60 minutes.			

❖ **Manuel calculation:**

$$\text{Zinc in } \mu\text{mol/l } (\mu\text{g/dl}) = \frac{\text{A sample} - \text{A blank}}{\text{A standard} - \text{A blank}} \times \text{Standard Conc} \mu\text{mol/l } (\mu\text{g/dl})$$

Normal value in serum: Adults 09.18 - 18.4 µmol/l (60 - 120 µg/dl)

1.3.2.3 Vitamin C measurement:

The reference range of vitamin C is (2-15 mg/l)

❖ **Principle of the method :**

An oxidation is induced prior to analysis so that both forms are measured (ascorbic acid and its oxidized form, dehydro-ascorbate). A dose response curve of the absorbance unit (optical density, OD at 492 nm) vs. concentration is generated, using the values obtained from the standard. The concentration of the specimen sample is determined directly from the linear standard curve.

❖ **Preparation and storage of reagents :**

- All reagents are stable at 2 °C - 8 °C up to the expiry date stated on of the label; except STD and CTRL at -20 °C;
- STD were reconstituted with 400 µl of ultra-pure water;
- CTRL1 and CTRL2 were reconstituted with each 250 µl of ultra-pure water;
- Allow the vial content to dissolve for 10 minutes at room temperature;
- Samples were kept cool and light-protected. Samples were measured within 24 hours after blood withdrawal.

➢ **Sample and reagent preparation**

- Pipette 200 µl prepared simple, reconstituted STD (standards) and CTRL1 and CTRL2 into Eppendorf cups, respectively, and add 200 µl PREC (precipitation reagent);
- Vortex well;
- Centrifuge at 10000 x g for 30 min.

➢ **Preparation of the working solution:**

To run a complete microtiter plate:

The working solution was prepared directly before the test and only the appropriate amount necessary for each assay: mix 10 volumes of SOL A (reagent solution A with each 1 volume of SOL B and C (reagent solution B and C)).

❖ **Assay procedure :**

1. Add 2 x 100 µl of the supernatants of STD (standard), CTRL1 and CTRL2 (control 1 and control 2) or samples into the PLATE (microtiter plate) wells in duplicates;
2. Add 50 µl of the freshly prepared working solution in the wells;
3. Cover the PLATE (microtiter plate) with foil and incubate for 3 h at 37 °C;
4. Add 150 µl of STOP (Stop Solution) in the wells;
5. Shake microtiter plate on a horizontal shaker at room temperature for 20 min (without any foil cover). An orange precipitate can be formed. The precipitate can be dissolved by repeatedly (2-3 times) drawing up the solution with the pipette;
6. Determine the absorption at 492 nm or 520 nm against 620 nm as a reference using ELISA reader.

2.4 Statistical analysis:

Analysis was performed using SPSS version 20 software for windows. Independent sample t-test was used for comparisons of the variables between the obese and non-obese individuals. P values were used to illustrate the degree of statistical significance. $P < 0.05$ was considered significant for all analysis.

3. Results:

The oxidative stress levels of 30 obese (BMI ≥ 30 kg/m^2) and 30 non-obese (BM < 25 kg/m^2) participants were compared by analyzing fasting blood samples.

The demographic and anthropometric features of evaluated groups are listed in table II.1. There were statistical differences *(P<0.05)* in the anthropometric values (weight, BMI and WC) between obese and non-obese groups, they were significantly greater in the obese group.
Individuals from both genders were categorized regarding their BMI as 18 individuals (60 %) with obesity class 1, 8 individuals (26.67 %) with obesity class 2 and 4 individuals (13.33%) with morbid obesity.

All other baseline variables were not different between groups, this result indicates balance between the groups and indicates equality, because the differences did not reach the significance level of a *P-value <0.05,* hence eliminating their confounding effect.

The mean age of the participants was 36.38 years, 71.67% of whom were women, which makes the groups of the study female-dominated [Table II.2]. Based on their age, subjects were divided into three subgroups: 46.67 % aged 18-32 years old, 33.33 % aged 33-47 years old, and 20% aged 48-62 years old [Table II.3].

Laboratory data are presented in table II.5. When classical biochemical parameters were compared, dyslipidemia was confirmed in obese group, the plasma cholesterol levels were significantly (*P*<0.05) increased in obese subjects compared with those of control subjects. However, there were no statistical differences in the other parameters (triglyceride and glucose) *(P>0.05).*

The oxidative stress parameters values are shown in table II.6 Higher oxidative stress in obese patients was confirmed by significantly elevated levels in copper/zinc ratio (*P*<0.05), the majority of control group had Cu/Zn ratio < 1.5, which wasn't the same for the obese group.
Furthermore, vitamin C levels were significantly (*P*<0.05) decreased in obese subjects.
Higher levels of oxidative stress markers also coincided with the lower levels of zinc when the groups were compared. There was no statistical difference in copper levels between obese and non-obese groups *(P>0.05).*

3.1 Demographic and anthropometric characteristics of the study groups:

Table II.1: Demographic and anthropometric features of study groups.

	Groups	N	Mean	T	P	P<0.05=*
Age (years)	Obese	30	37,00	0,282	**0,389**	
	Non obese	30	35,77			
Weight (kg)	Obese	30	95,2000	11,167	**0,000**	*
	Non obese	30	62,2333			
Height (m)	Obese	30	1,6343	-1,477	**0,072**	
	Non obese	30	1,6610			
BMI (kg/m²)	Obese	30	35,7297	13,485	**0,000**	*
	Non obese	30	22,4860			
WC (cm)	Obese	30	112,0167	8,836	**0,000**	*
	Non obese	30	82,2667			

* = statistically significant differences with group 1 and 2 ($p< 0.05$)

Table II.2: Sex distribution in the study groups.

Sex	No.	Percent
Male	**17**	**28.33 %**
Female	**43**	**71.67 %**
Total	**60**	**100 %**

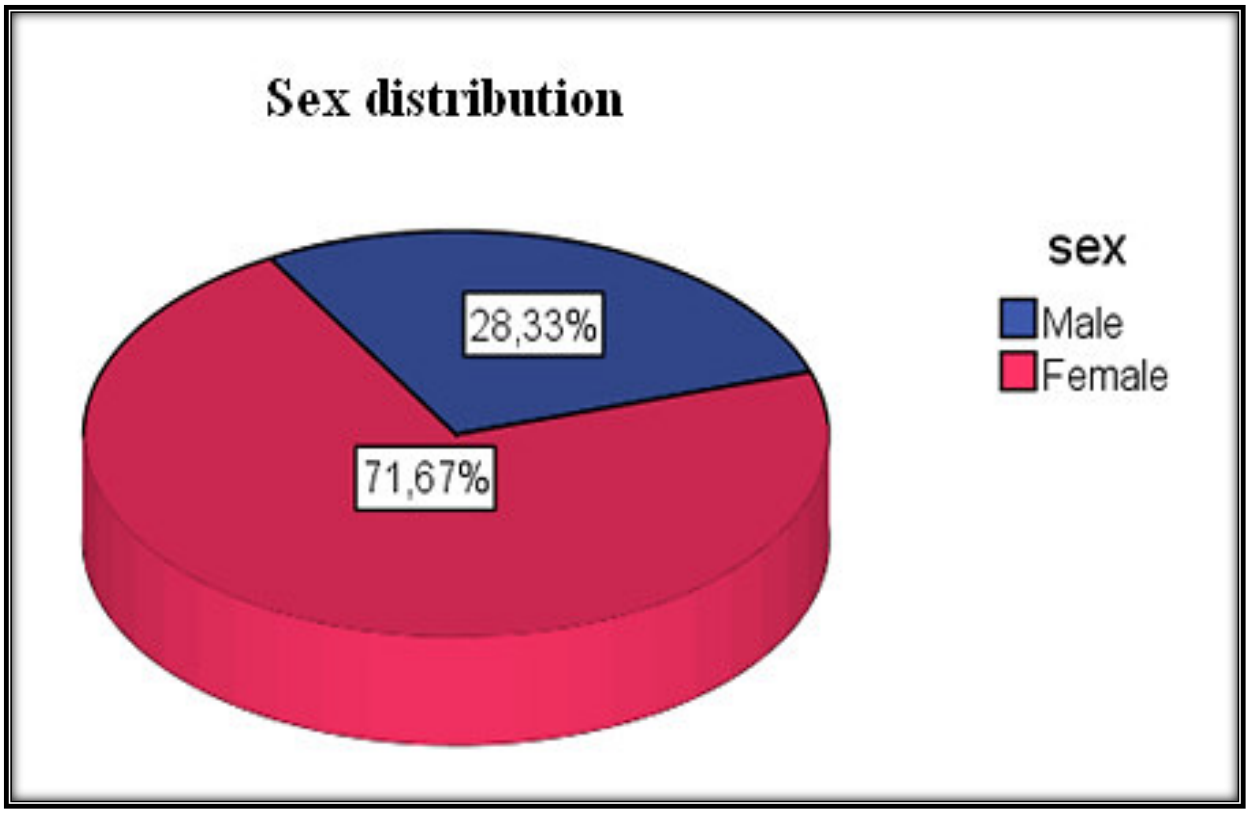


Figure II.1: **Sex distribution in the study groups**.

This case-control study included 60 individuals with obese (obese group) and non-obese (normal weight group) consisted of 17 men (28.33 %) and 43 women (71.67 %), therefore female-dominated.

Table II.3: Age distribution in the study groups.

Age groups	No.	Percent
18-32	**28**	**46.67 %**
33-47	**20**	**33.33 %**
48-62	**12**	**20.00 %**
Total	**60**	**100 %**

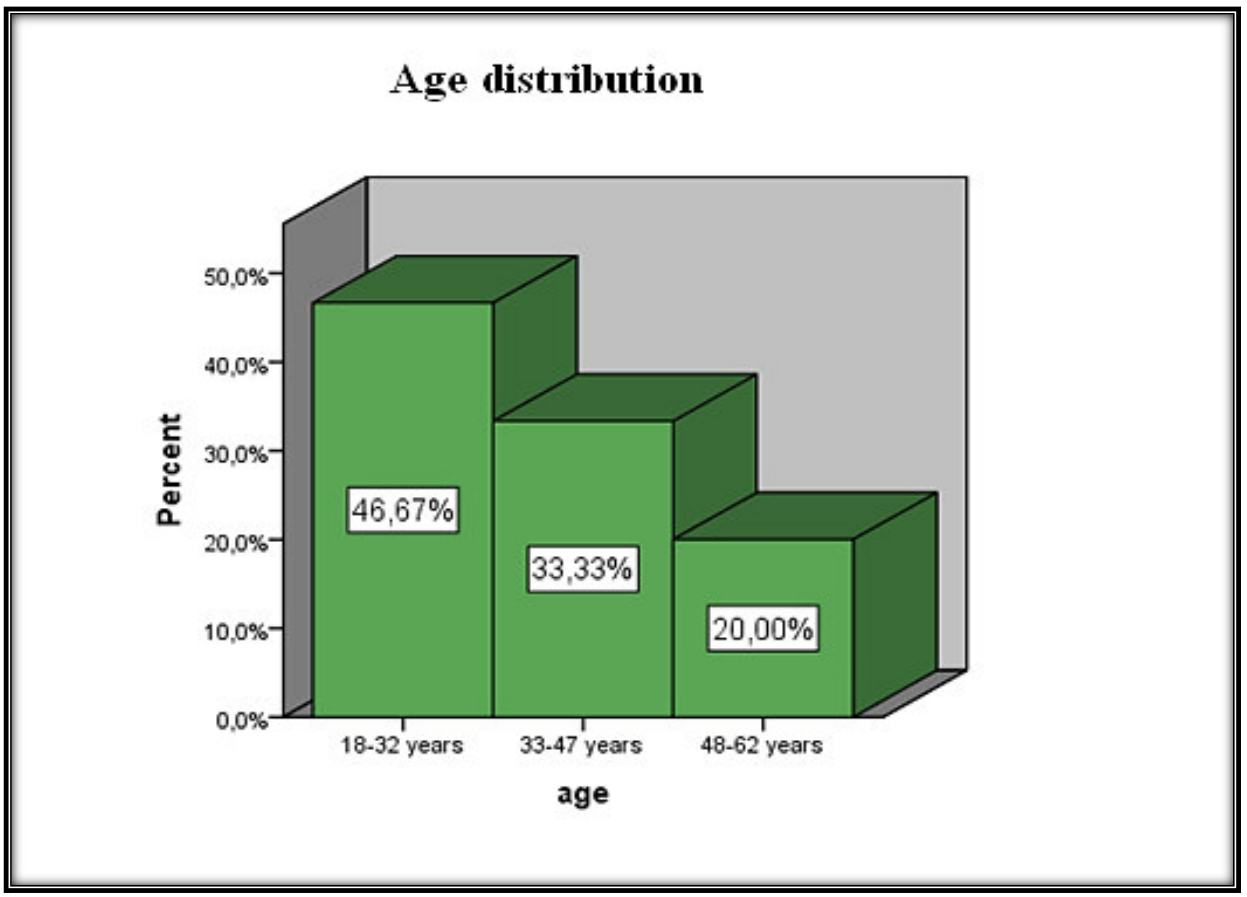


Figure II.2: **Age distribution in the study groups.**

The age of the study subjects ranged from 18 to 62 years with a mean age of 36.38 years. For graphic presentation, participants were classified according to three age groups as 28 individuals (46.67 %) aged 18-32 years old, 20 individuals (33.33 %) aged 33-47 years old, 12 individuals (20.00 %) aged 48-62 years old.

Table II.4: BMI distribution in the obese group.

BMI groups	No.	Percent
30 to less than 35 kg/m^2	18	60.00 %
35 to less than 40 kg/m^2	8	26.67 %
40 kg/m^2 and over	4	13.33 %
Total	30	100 %

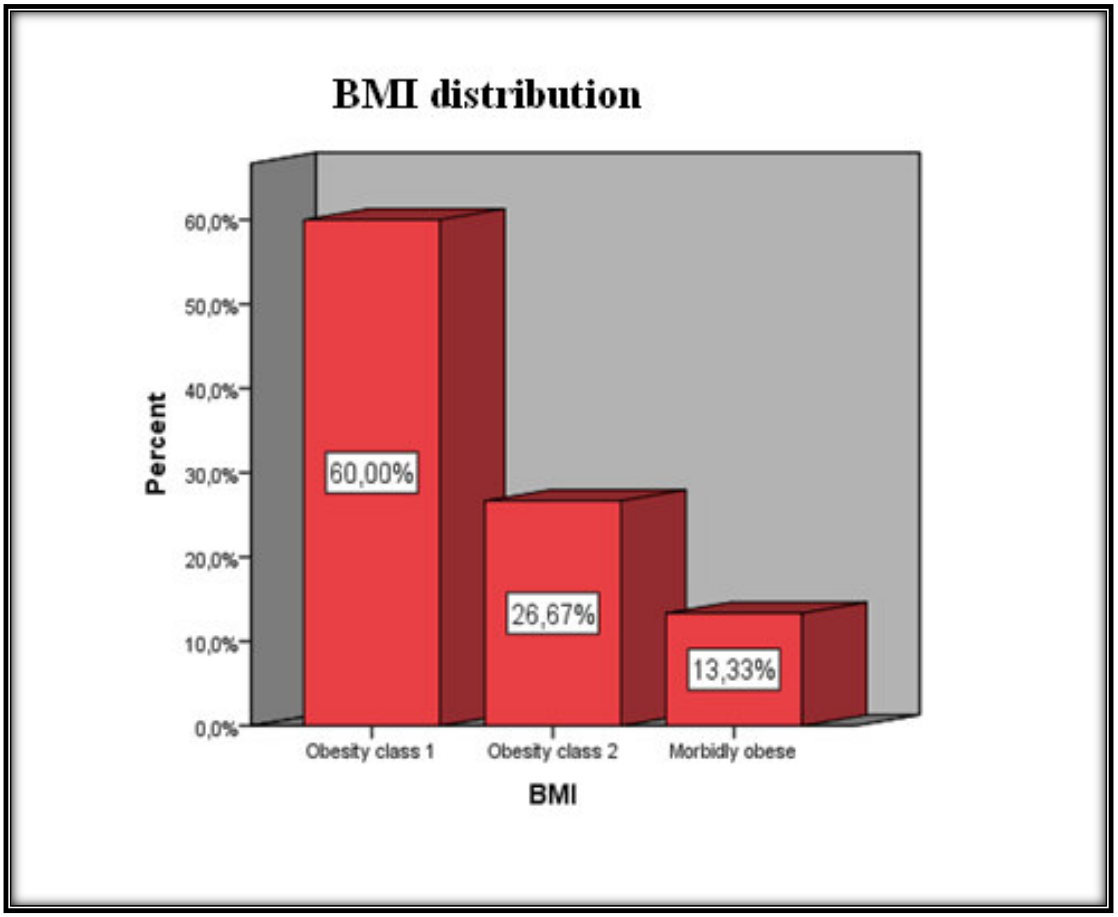


Figure II.3: Distribution of obese group according to their BMI using the WHO classification.

Class I obese (BMI, 30 to 34.9 kg/m^2); class II obese (BMI, 35 to 39.9 kg/m^2); morbidly obese (BMI ≥40 kg/m^2). Individuals from both genders were categorized regarding their BMI as 18 individuals (60 %) with obesity class 1, 8 individuals (26.67 %) with obesity class 2 and 4 individuals (13.33%) with morbid obesity.

3.2 Comparison of biochemical parameters (triglycerides, total cholesterol and glucose) between the obese and the control groups:

Classical biochemical parameters were determined in both groups of the study. The plasma cholesterol levels were significantly ($P<0.05$) higher in obese subjects compared with those of control subjects, as table II.5 shows. However, there were no statistical differences in the other parameters (triglyceride and glucose) *($P>0.05$).*

Table II.5: Basic biochemical parameters of the study groups.

	Groups	N	Mean	T	P	P<0.05=*
Triglycerides (mg/dL)	Obese	30	1,3833	1,638	0,053	
	Non obese	30	1,1093			
Total cholesterol (mg/dL)	Obese	30	1,9830	4,592	0,000	*
	Non obese	30	1,4880			
Plasma glucose (mg/dL)	Obese	30	0,9757	0,674	0,251	
	Non obese	30	0,9453			

* = statistically significant differences with group 1 and 2 ($P< 0.05$)

3.3 Comparison of the level of oxidative stress markers between the obese and control subjects:

To evaluate the oxidative stress, vitamin C, zinc and copper/zinc ratio where chosen as biomarkers, then, were measured in both groups of this study and their levels are showed in table II.6. Higher oxidative stress in obese patients was confirmed by significantly elevated levels in copper/zinc ratio ($P<0.05$), and significantly lower levels in vitamin C and zinc.

Table II.6: Oxidative stress status according to study groups.

	Groups	N	Mean	T	P	P<0.05=*
[Vit C] mg/l	Obese	30	6,1597	-3,852	0,000	*
	Non obese	30	9,6643			
[Cu] µmol/l	Obese	30	19,4970	2,576	0,065	
	Non obese	30	16,1013			
[Zn] µmol/l	Obese	30	11,5203	-5,156	0,000	*
	Non obese	30	15,0527			
[Cu] / [Zn]	Obese	30	1,7437	5,911	0,000	*
	Non obese	30	1,0987			

* = statistically significant differences with group 1 and 2 ($P< 0.05$)

3.3.1 Comparison of serum vitamin C levels detected in obese and control groups:

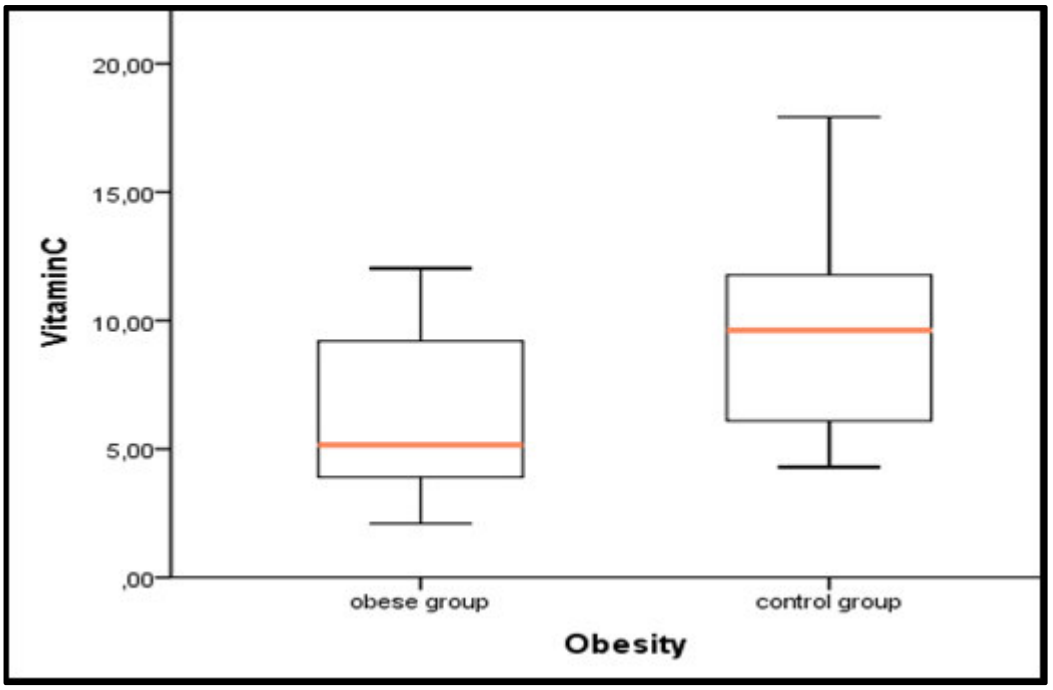


Figure II.4: Box plots comparing means levels of vitamin C in obese and non-obese subjects.

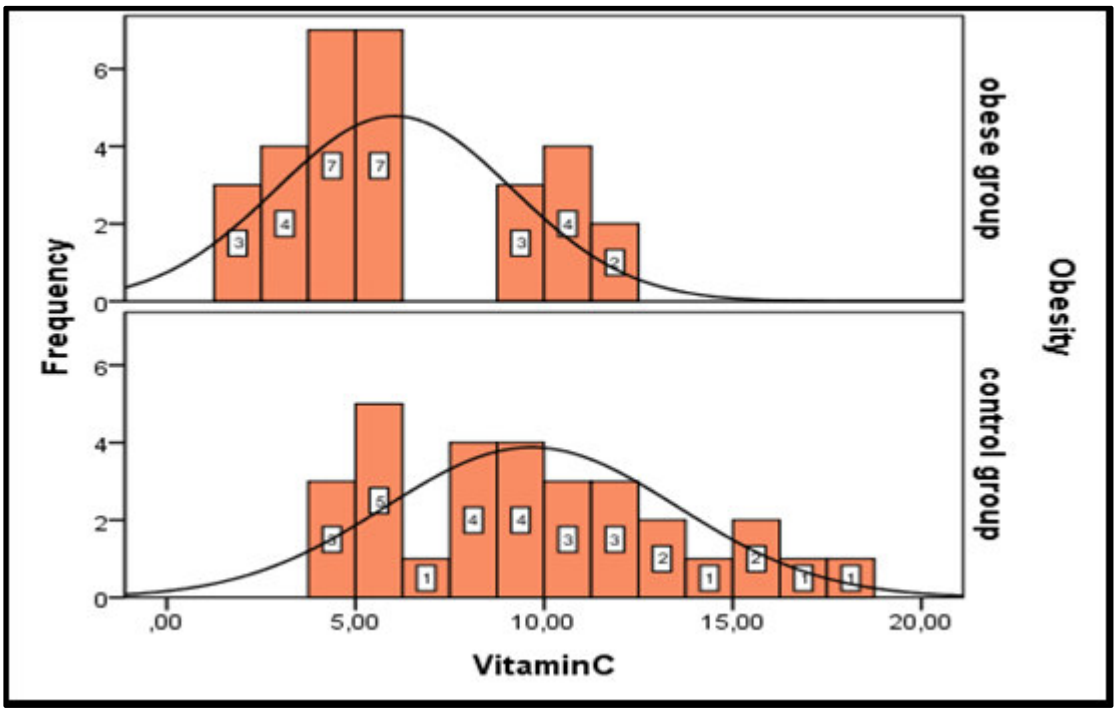


Figure II.5: Frequency distribution histograms of vitamin C levels in obese and non-obese subjects.

3.3.2 Comparison of serum copper levels detected in obese and control groups:

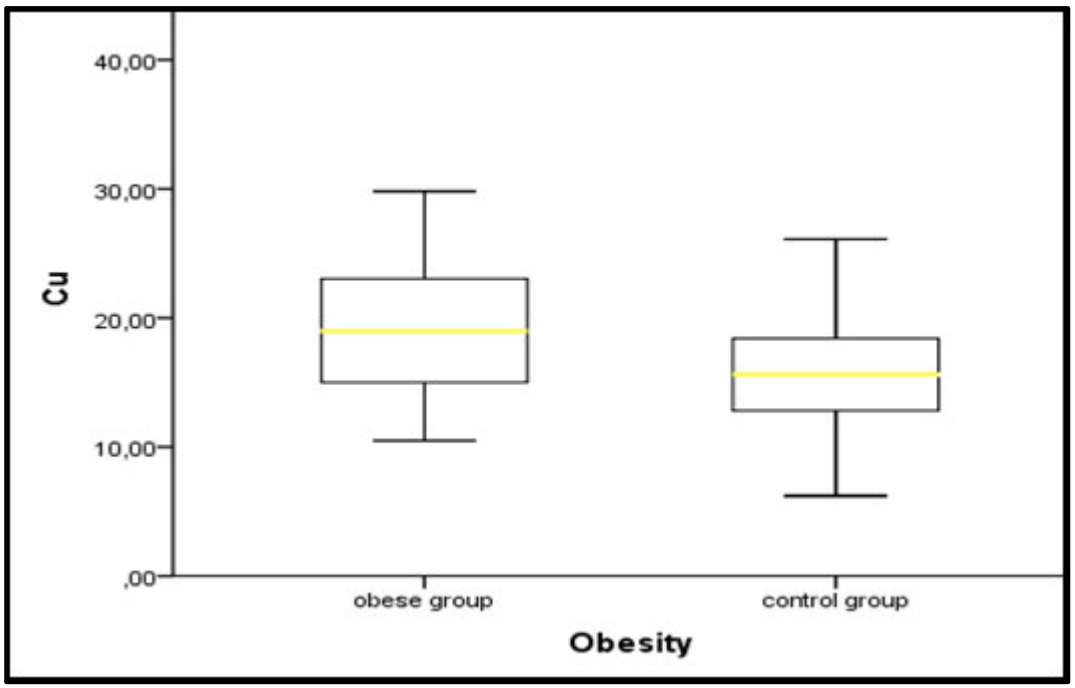


Figure II.6: Box plots comparing means levels of copper in obese and non-obese subjects.

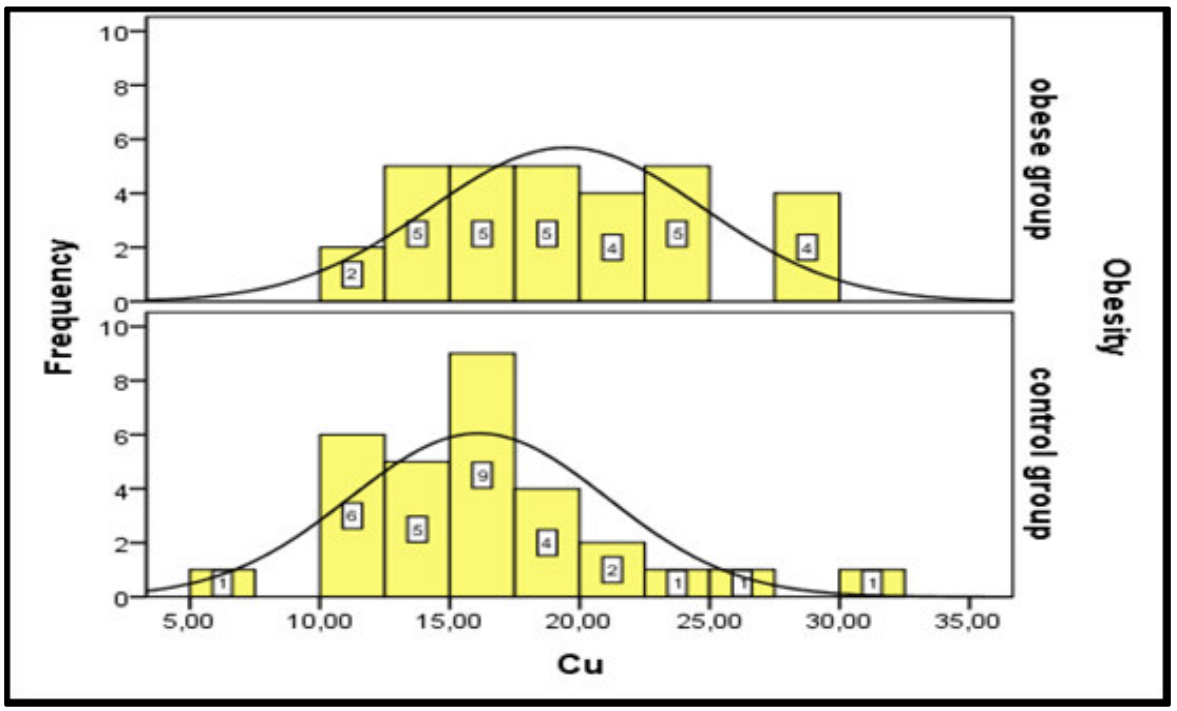


Figure II.7: Frequency distribution histograms of copper levels in obese and non-obese subjects.

3.3.3 Comparison of serum zinc levels detected in obese and control groups:

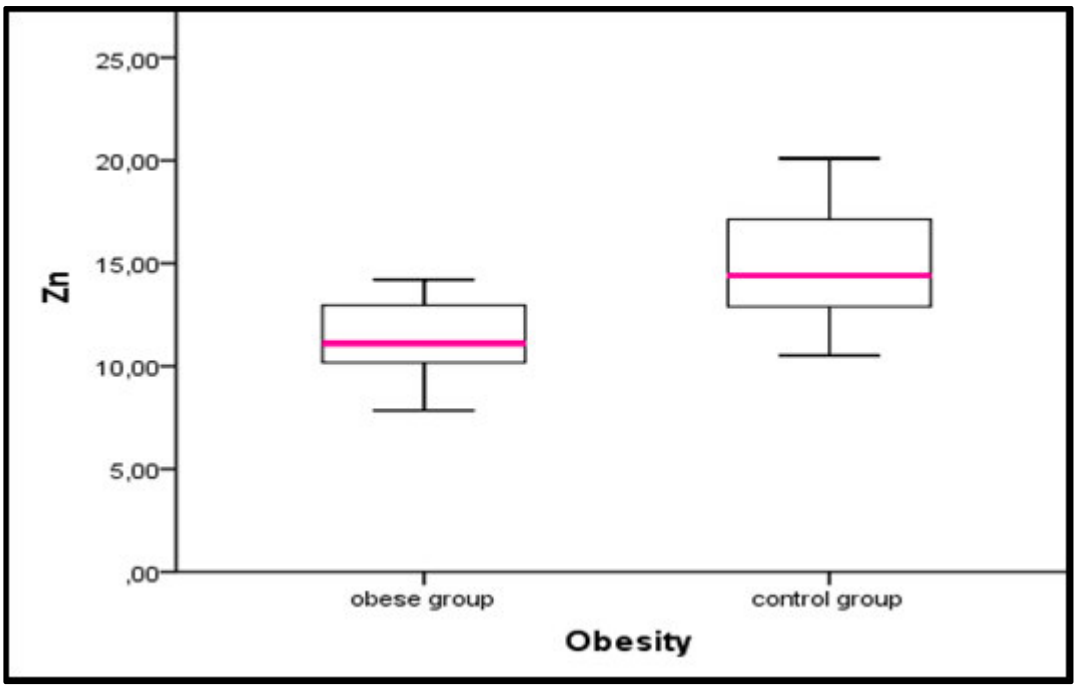


Figure II.8: Box plots comparing means levels of zinc in obese and non-obese subjects.

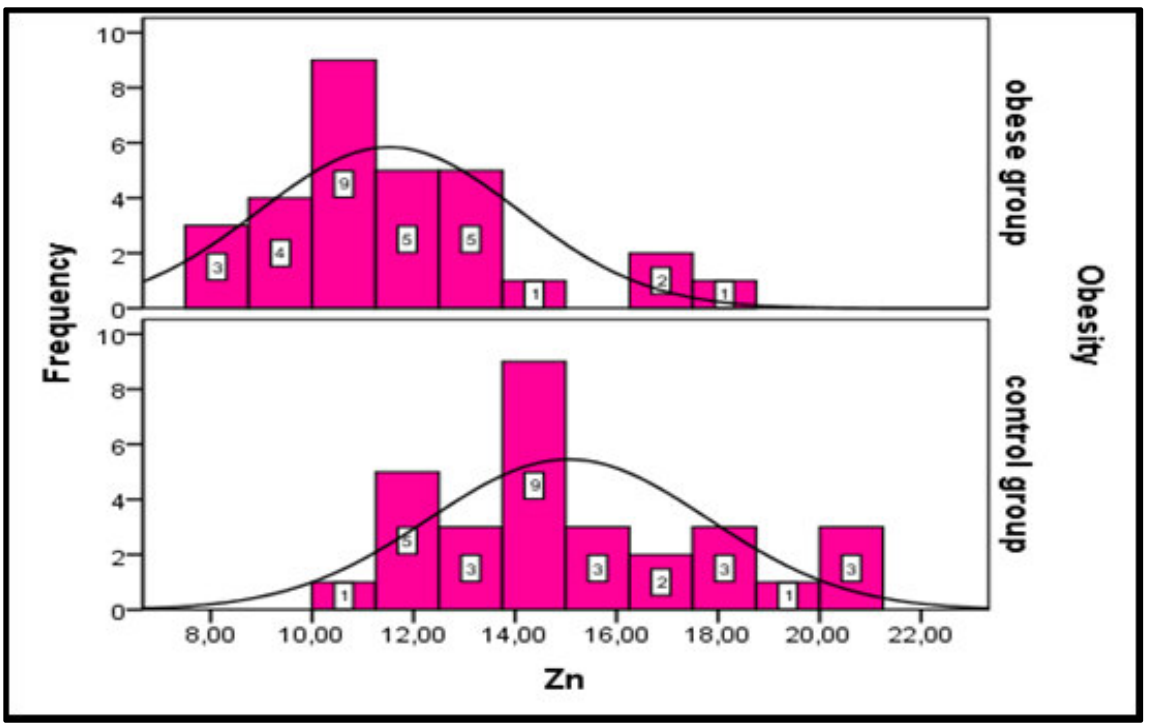
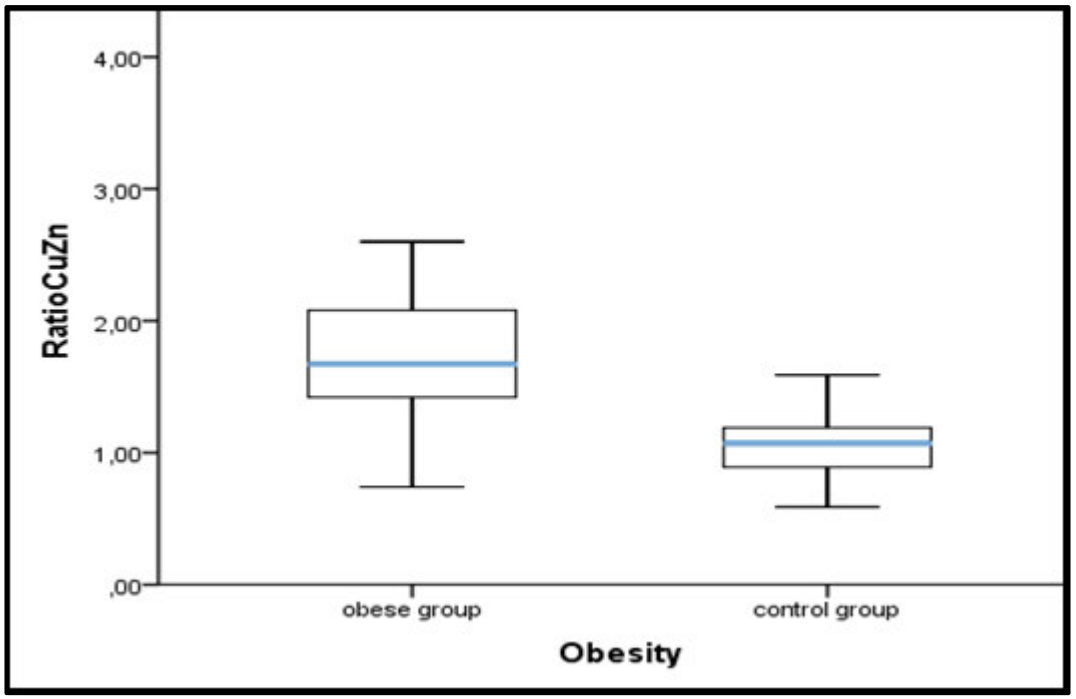


Figure II.9: Frequency distribution histograms of zinc levels in obese and non-obese subjects.

3.3.4 Comparison of ratio copper/zinc levels detected in obese and control groups:



p **Figure II.10: Box plots comparing means levels of Cu/Zn ratio in obese and non-obese subjects.**

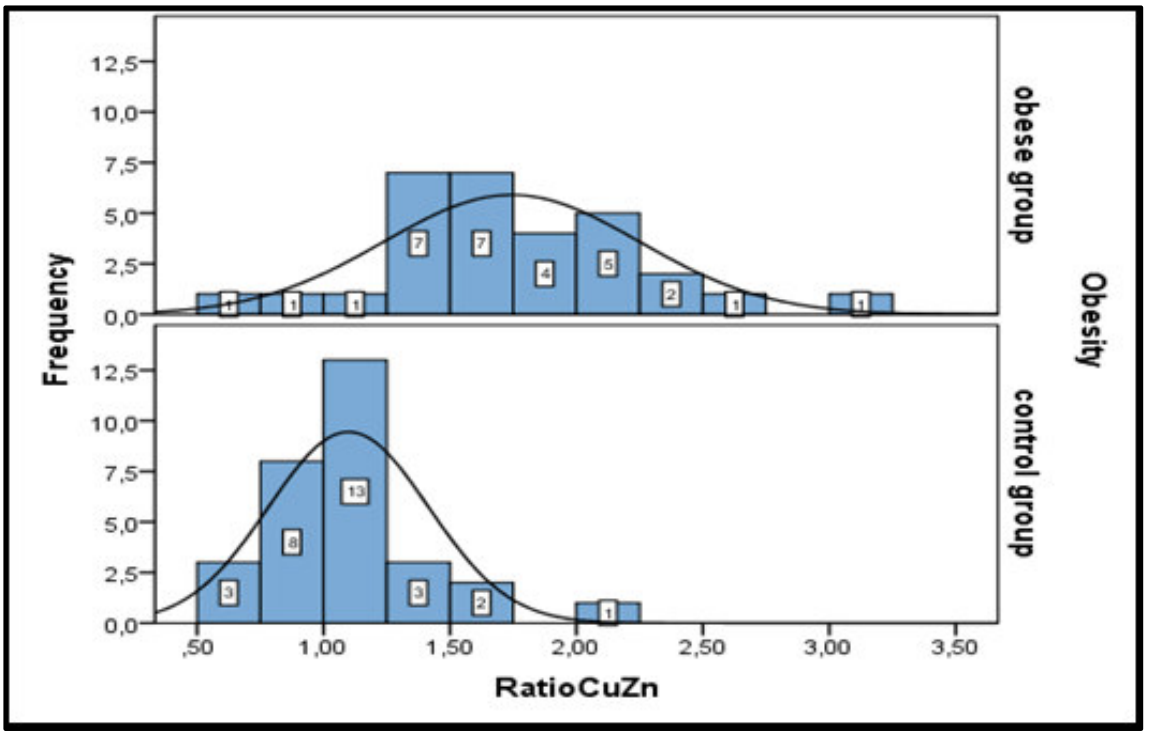


Figure II.11: Frequency distribution histograms of Cu/Zn ratio levels in obese and non-obese subjects.

4. Discussion:

Obesity has become a leading global health problem owing to its strong association with a high incidence of diseases. It is a chronic disease of multi-factorial origin affecting both adults and children. Weight excess results from an imbalance between food intake and energy expenditure, which leads to an excessive accumulation of adipose tissue. Excess caloric consumption and a sedentary lifestyle are the recognized risk factors favoring obesity.

The anthropometry of the subjects suggests that obesity and fat distribution may be the key factors of oxidative stress in the subjects.

In this study, vitamin C, copper and zinc were measured as biomarkers of oxidative stress in order to investigate how obesity influences their levels.

❖ Zinc:

In the present study, a significant difference between the two groups ($P < 0.05$) was observed with regard to the results of serum zinc concentrations; where obese group has lower levels of serum zinc, these results agreed with those of previous studies that showed a reduced plasma zinc concentration in obese individuals [126, 127, 128].

Changes in plasma zinc levels in obesity were first demonstrated in a study conducted by Atkinsons et al. [129] in 1978. The study included 15 obese individuals compared to 52 controls. Other studies about the role of zinc in obesity were published [130, 131]; some of them demonstrated a significant reduction in the concentration of zinc in plasma in obesity [132, 128].

Serum trace elements, including zinc, and their link with obesity were studied by many authors [133, 134]. In order to better understand the metabolic behavior of zinc in obesity some studies have used more sensitive markers, such as erythrocytes, for assessing the nutritional status of this mineral. Ennes Dourado Ferro et al. [135] investigated the relationship between metabolic syndrome and zinc status in obese women and found decrease erythrocyte zinc level in their obese subjects; these results are consistent with those already found by Marreiro et al. [136] in a study of obese children and adolescents and by Ozata et al. [121] in obese adult men.

Zinc, in particular, has been the element of greatest interest to many researchers. The diagnosis of zinc nutritional status is considered a challenge, because a sensitive practical specific method for zinc determination is still unavailable. As a result, the association of several indices has been the most suitable way for obtaining more accurate results [137].

The zinc pool is normally well regulated and enables conditions to maintain the mineral homeostasis in the body. Determination of plasma zinc is the most used index for the assessment of the mineral nutritional status [137]. It is transported in plasma and is associated mainly to albumin, 2-α macroglobulin, and amino acids, especially histidine and cysteine [138].

Zinc is of critical importance in certain metabolic pathways, acting as a cofactor for numerous enzymes in the metabolism of carbohydrates, proteins, and lipids. It also plays a catalytic and structural role in tissue formation and hormone receptor activation [139]. It takes part in the metabolism of hormones involved in the pathophysiology of obesity. Zinc plays a major role in the stabilization of insulin hexamers and the storage of hormone in the pancreas [140].

It has been observed that zinc concentration is directly associated with serum leptin concentration [130], an adipokine associated with satiety [141]. This association could be explained by the effect of zinc-α2-glycoprotein (ZAG) on leptin concentrations. ZAG is an adipokine involved in lipolysis in the adipocyte that is down-regulated in obesity. In obese individuals, low ZAG gene expression is associated with low serum adiponectin and high plasma leptin levels, and may play an important role in the pathogenesis of obesity [142]. Chen et al. [143] suggested in their study that leptin resistance that occurred in obesity might have resulted from zinc deficiency.

Zinc is an efficient antioxidant [144], its role in modulating oxidative stress has recently been recognized [145, 146]. It is an inhibitor of one of the most significant intracellular sources of ROS, NADPH oxidases which are a group of plasma membrane associated enzymes that catalyze the production of $\cdot O_2^-$ from oxygen by using NADPH as the electron donor.

Zn treatment is postulated to cause an increase in H_2O_2 concentration and a decrease in ·OH concentration [147] by interfering with the redox capacity of iron and copper ions which catalyze the production of ·OH from H_2O_2. Zinc is known to compete with both iron and copper for binding to the cell membrane, thus decreasing the production of ·OH [148].

Zn ions inhibit electron transport in both mitochondrial and microsomal electron transport chains. In isolated mitochondria, Zn inhibits the electron transport between ubiquinone and cytochrome b in an uncoupled system. The effect is reversible and is apparently caused by Zn binding to cytochrome b or to a protein that modulates cytochrome b function. This effect also occurs in coupled mitochondria at a slightly higher Zn concentration [149]. The dismutation of $\cdot O_2^-$ to H_2O_2 is catalyzed by an enzyme, SOD, which contains both copper and zinc as cofactors. The action of zinc by the activation of superoxide dismutase is beneficial in repairing the damage caused by oxidative stress at the cellular level. Zinc is known to induce

the production of metallothionein, which is very rich in cysteine and is an excellent scavenger of ·OH [150].

Despite the known multiple biochemical roles of zinc as an antioxidant, most studies have been done using cell lines or animals and very few studies have investigated the use of zinc in the management of oxidative stress in humans [148].

The inflammatory cytokines such as TNF-α and IL-1, generated by activated monocytes–macrophages, are also known to produce increased amounts of ROS [151].

Increases in these inflammatory cytokines are associated with decreased zinc nutritional status in adult overweight/obese subjects [152] and increased lipid peroxidation products are associated with decreased zinc status in children with chronic giardiasis [153].

Prasad et al. have reported that zinc supplementation to normal healthy subjects lowered the oxidative stress-related by-products malondialdehyde (MDA), 4-hydroxyalkenals and 8-OHdG generated by cells and released into the plasma, inhibited the induction of TNF-α and IL-1b mRNA in mononuclear cells, and exhibited a protective effect against TNF-a induced NF-κB activation in isolated mononuclear cells [148]

The effects of 30 mg zinc (as gluconate) supplementation on oxidative stress in 56 Tunisian adult subjects with type-2 diabetes mellitus were evaluated. Following 6 months of zinc supplementation, plasma zinc increased and plasma oxidative stress markers were significantly decreased, whereas the placebo group showed no such changes [154].

The effects of vitamin C and zinc supplementation on osmotic fragility and lipid peroxidation of erythrocytes were studied in 34 zinc deficient hemodialysis patients [155]. Patients were randomized to receive vitamin C (250 mg daily), zinc (20 mg daily) or a placebo treatment for 3 months. Supplementation with vitamin C and zinc improved osmotic fragility and decreased the level of the plasma lipid preoxidation product MDA.

Recently, in a large study organized by the National Eye Institute, it was reported that zinc and antioxidants (vitamin C, vitamin E and beta carotene) significantly reduced the odds of developing advanced age-related macular degeneration and prevented blindness in the high-risk group of elderly subjects [156].

Although the mechanism of zinc effect was not defined, one may hypothesize that zinc reduced the oxidative stress and was thus beneficial in age-related macular degeneration. Another interesting observation was reported that only the zinc supplemented group showed increased longevity [157].

From the above results, the elevated levels of pro-inflammatory cytokines in serum of obese subjects and increased oxidative stress accompanied with decreased antioxidant defense

mechanisms as well as hypozincemia play an important role in the development of obesity-related complications. Moreover, zinc deficiency may contribute to increased inflammation and susceptibility to related diseases.

- **Copper:**

Our data show no significant difference in serum copper levels between obese and normal subjects. These results are comparable to other studies [158].

The assessment of erythrocyte Cu can be considered a safe biomarker, as these cells do not suffer the influence of inflammatory and hormone alterations. Erythrocyte Cu variations occur more slowly, whereas plasma Cu might be influenced by diet and circadian variations [159].

Recent interest in determining copper content has been aroused by the observation of metabolic anomalies present in a number of diseases (such as obesity) and the interest in the role that deficiency/excess of minerals may play in these disease processes [160].

Cu is a component of antioxidant enzymes that act to protect the body against the action of free radicals, especially in cardiovascular diseases. An imbalance in the metabolism of Cu might trigger hypercholesterolemia and disorders in oxidative stress [161]. In trace element metabolism the best known interaction is the reported antagonism between zinc and copper [162]. Copper is not only a ubiquitous metal in the technological environment, it is also essential for the function of most living organisms [163]. In the same way that it allows the movement of electrons through wires, it also helps catalyze the movement of electrons within biological molecules. Equipped with a high redox potential, copper serves as a cofactor for proteins involved in a variety of biological reactions, connective tissue formation, iron metabolism, free radical eradication and neurological function [164].

The present study showed that serum Cu levels in the obese were not significantly higher than those in healthy controls ($P > 0.05$). This disagreed with Lima et al. who reported that copper concentrations in plasma in the overweight and obese groups were significantly higher than those in the control group [165], and was also verified by Pino et al. [166] and Tungtrongchitr et al [167]. In another prospective study in Tunisia, the serum copper levels were evaluated by atomic absorption in a group of 32 obese compared to a group of 32 healthy subjects serum level of copper was evaluated in a group of 32 obese (BMI $\geq$ 30 kg/m^2) compared to a group of 32 healthy subjects. A significate elevation of serum copper in obese has been noted. In another hand, the authors noticed that the levels of serum copper rise with the BMI [168].

Considering all of the findings together, it is supplied that the ratio of serum Cu/Zn ratio levels, instead of serum zinc levels alone provides more useful information [169].

The results found by the authors mentioned above, suggest that excess weight associated with lipid metabolism disorders might predispose to changes in Cu concentrations in plasma indicating a possible mechanism of this mineral, contributing to peroxidation or acting as an antioxidant. The pro-oxidant capacity of Cu, once activated, predisposes LDL-c lipoperoxidation, which suggests an intrinsic relation with lipid profile alterations [170]. The inverse correlations between Cu and lipid fractions identified in the study of Lima et al. The interrelation of the results obtained in their study lead to speculations that must guide investigations on the complications of obesity, not only those attributed to the lipid profile and diet but also to Cu disturbances exacerbating the harmful effects of lipoperoxidation. Excess weight has been considered a causal factor of lipid peroxidation and of decreased antioxidant enzymes [171].

Copper, in excess of cellular needs, mediates free radical production and direct oxidation of lipids, proteins, and DNA. Therefore the balance between intracellular and extracellular contents of copper is driven by cellular transport systems that regulate uptake, export and intracellular compartmentalization [172]. The balance between copper necessity and toxicity is achieved both at the cellular level and at the tissue and organ levels [173].

Cells regulate the traffic of transition metal ions (such as copper and iron), maintaining the amount necessary for biological function while avoiding excess levels that are toxic. Among the factors required to achieve such metal ion homeostasis are the metallochaperones, proteins that, like chaperones in ordinary life, guide and protect transition metal ions within the cell, delivering them safely to the appropriate protein receptors. “Metallo-Chaperones” can also prevent dangerous reactions that can cause damage to the cell [174].

Until recently, it had been commonly believed that metal ions were in equilibrium with metalloproteins; however, their results suggest that there is a significant overcapacity for chelation of copper in the cell and there must be multiple processes that bind the copper and prevent it from ever being randomly available. The implications of this finding are profound, especially if applicable to other physiologically important transition metals. This discovery has wide implications on the mechanisms of intracellular formation of free radicals by means of Fenton chemistry [173]. One of the most accepted explanations for copper-induced oxidative stress is that cellular toxicity comes from the assumption that copper ions are prone to participate in the formation of reactive oxygen species (ROS). Cupric and cuprous copper ions can act in oxidation and reduction reactions. The cupric ion (Cu(II)), in the presence of biological reductants such as ascorbic acid or GSH, can be reduced to cuprous ion (Cu(I))

which is capable of catalyzing the formation of reactive hydroxyl radicals (·OH) through the decomposition of hydrogen peroxide (H_2O_2) via Fenton reaction [173].

$Cu(I) + H_2O_2 \rightarrow Cu(II) + \cdot OH + OH$

- **Copper/zinc ratio:**

Copper and zinc as trace elements are necessary in small concentrations as essential constituents of biological enzyme systems [175]. These two metals together have a significant influence on immune functions [176] and play a central or putative role in the development of important age-related diseases, including CVD [105], cancer [177], type 2 diabetes [178, 179] and Alzheimer's disease [180]. Plasma concentration of these trace elements is affected by physiological conditions such as age, gender and nutritional status, as well as by pathophysiological conditions, like inflammation and the presence of cardiovascular risk factors [181].

Although the clinical potential of Cu to Zn ratio has been extensively investigated, few authors addressed the mechanisms that mainly contribute to the increase of Cu/Zn ratio in serum during aging, which signals drive, this change and how cells respond to these changes.

Copper and zinc serum concentrations are strictly regulated by compensatory mechanisms that act to stabilize them within certain ranges of nutritional intake. However, there are mechanisms that are built to decrease serum concentration of Zn and to increase serum concentration of Cu in the presence of inflammatory conditions, so that a common feature of several age-related chronic diseases is an increase of Cu/Zn ratio [182].

The decrease in serum zinc concentration is often accompanied by an increase in copper level [183]. Accordingly, several studies have reported elevated serum copper levels during aging [184, 185]. In this study, there was a statically significant difference between the two groups where obese had higher copper to zinc ratio than the normal subjects. These results were confirmed by other studies and a statistically significant positive correlation between levels of plasma leptin and the Cu/Zn ratio was established [175]. Olusi et al. documented that serum leptin levels were positively correlated with Cu and the Cu/Zn ratio [186].

Zinc and copper are mineral nutrients known to participate in several antioxidant systems, including metalloproteins, such as the copper-zinc enzyme superoxide dismutase and the low-molecular weight zinc- and copper-binding protein metallothionein [187]. Superoxide dismutase acts reducing the toxicity of oxygen reactive species by transforming the free radical superoxide ion into hydrogen peroxide that is less harmful to cells. Metallothionein is a cysteine-rich, free-radical scavenging protein related to cell zinc metabolism and

homeostasis [188]. Regulation of metallothionein synthesis depends on an adequate nutritional zinc status [189]. Metallothionein appears to have antioxidant properties in a diversity of conditions such as exposure to radiation, drugs, heavy metals, and physiological stress [188]. Erythrocyte metallothionein has been measured in humans in response to changes in zinc intake [190] and in special physiological conditions such as pregnancy [191].

Increased oxidative stress in aging and age-related disorders could play a major role in raising the levels of Cu/Zn ratio by both decreasing plasma Zn and increasing plasma Cu. It has been shown that the albumin bound fraction of Zn decreases in the plasma while labile Zn is loaded to peripheral tissues during some forms of oxidative stress [192]. Indeed, physiological and pathological changes in the redox state of human serum albumin critically influence its binding properties [193]. The Zn ions displaced from albumin by increased oxidative stress are subsequently delivered into cells and tissues by specific transporters [194]. Therefore, oxidative stress can contribute to decrease levels of plasma Zn without a necessary concomitant decrease of albumin levels. The labile Zn loaded into peripheral tissues displays several functions among which emerges the induction of the potent antioxidant protein metallothioneins [195]. A strong response to increasing oxidative stress is also a feature of serum Cu [106].

Concomitantly, another factor that contributes to an increase in plasma Cu/Zn ratio with advancing age is the progressive decline of plasma Zn. This phenomenon may occur due to decreased dietary intake, reduced absorption [196] and altered compartmentalization caused by chronic low-level inflammation [197]. Indeed, pro-inflammatory cytokines, such as IL-6, stimulates Zn uptake and metallothionein expression in different tissues and cells [198]. Given the pivotal role played by metallothioneins in retaining intracellular Zn with the subsequent reduction of plasma Zn [198], higher Cu/Zn ratio plasma levels might in part reflect this phenomenon.

Therefore, multiple factors could contribute to raising plasma Cu/Zn with ageing, including chronic low-level inflammation [178], impaired nutritional status [199] and specific underlying conditions which increase the risk of mortality, such as CVD [200].

In this study, higher Cu/Zn ratio in obese group was noticed what makes us suggesting that it may be a sign of an increase oxidative stress in obese individuals.

❖ **Vitamin C:**

Some studies have found that obese individuals are characterized by micronutrient deficiencies [201, 202] and antioxidants, such as vitamin C, and vitamin E [203, 204]. Similarly, in the present study there was a decrease in vitamin C concentrations in obese subjects when compared to the other groups.

The inverse relationship between plasma vitamin C and adiposity has been documented in several reports. In 1989, Schectman et al. [205] noted a significant inverse relationship between BMI and plasma vitamin C concentrations among 11592 participants. More recently, abdominal obesity, as measured by waist circumferences, was inversely related to plasma vitamin C among 19000 adults participating in the European Prospective Investigation into Cancer and Nutrition Norfolk cohort study [206]. This relationship remained significant after adjusting for age, BMI, vitamin supplement use, cigarette smoking, and social class.

Galan et al. have found lower vitamin C concentration in obese participants; moreover in the study of García et al. [134] low vitamin C concentrations were associated with obesity and with higher leptin concentrations. When stratifying, high leptin concentrations were associated with lower zinc and vitamin C concentrations in women with obesity and with high body fat percent, it has been observed that vitamin C dose-dependently inhibits leptin secretion in primary rat. A major limitation of this study is that cross-sectional studies cannot establish causality.

Other studies have found reduced serum concentrations of antioxidant vitamins in obese people [207, 208], but it is not known for sure whether adiposity reduces vitamin concentrations, perhaps a result of increased oxidative stress or dietary differences, or whether vitamins influence lipid accumulation in the adipocyte.

The most probable theory is that vitamin C reduces adiposity [209]; it may do that through a number of different mechanisms. Ascorbic acid has been shown to modulate adipocyte lipolysis [210, 211], inhibit inflammatory response [212] and inhibit leptin concentration [213]. Supplementing rats with vitamin C reduced the circulating levels of leptin and decreased body weight and adiposity in a rat model [214].

Vitamin C is a cofactor required for the biosynthesis of carnitine, a metabolite required for the transport of long chain fatty acids across the mitochondrial membrane for subsequent fat degradation and oxidation [215].

Carnitine deficiency is associated with reduced fat oxidation and lipid accumulation in muscle [216]; moreover, carnitine supplementation (3 g/day for 10 days) has been demonstrated to increase fat oxidation by 20% in slightly overweight subjects [217]. Muscle carnitine is

reduced substantially in vitamin C depletion [218], and reduced muscle carnitine may hinder fat oxidation contributing to obesity in some individuals [217, 219].

Ascorbic acid is regarded as the most important water-soluble antioxidant in human plasma and mammalian cells which have mechanisms to recycle and accumulate it against a concentration gradient, suggesting that the vitamin might also have important intracellular functions [81].

Vitamin C is one of the most widely used dietary supplements due to its antioxidant properties. The ability of vitamin C to reduce and neutralize ROS has been widely described [220]. In a placebo-controlled study where 369 of nonsmokers were randomized to 1000 mg/day vitamin C, or placebo, for two months, it has been proved that vitamin C reduced in vivo lipid peroxidation as measured by plasma F2-isoprostanes by 10.56%, which makes it a powerful antioxidant [221].

These beneficial effects could be explained by the stimulation exerted by this vitamin on MnSOD activity, suggesting that $\cdot O_2^-$ is rapidly converted into H_2O_2. Previous studies have shown that the protective role of vitamin C against oxidative stress is mediated by the stimulation of major mitochondrial antioxidant enzymes [222, 223]. The beneficial effects of vitamin C on oxidative damage can also be justified by its capacity to modulate H_2O_2 production, as demonstrated in several studies [224]. Vitamin C exerts these positive effects on mitochondrial redox state by inducing the activity of the electron transport chain, as found by Mandl et al. [225]. This increase in the electron transport chain activity gives support to findings concerning to the decrease in $\cdot O_2^-$ levels observed in isolated mitochondria treated with vitamin C. Furthermore, this increase in electron transport chain activity provides electrons to ascorbic acid in order to be transformed into dehydroascorbic acid, as previously proposed by Mandl et al. [225]. In addition, several studies have reported that vitamin C is a natural scavenger of ROS [226], being able to increase MnSOD and GPx expression and activity, [227, 223] which, in turn, leads to a decrease in superoxide and hydrogen peroxide production, respectively. The capacity of this antioxidant to reduce ROS levels has been proposed as a mechanism that could explain its protective role against situations with an imbalance in the oxidative status [228].

❖ **Cholesterol:**

Oxidative stress plays a crucial role in disorders related to obesity, such as dyslipidemia and hypertension, causing cardiovascular diseases. In the current study, serum levels of total cholesterol were significantly higher in obese subject than those with normal BMI. The results agreed with those of other authors who showed an increased level of cholesterol in obese subjects compared with control [229, 230]. Obesity is linked to an increased prevalence of dyslipidemia witch is a widely accepted risk factor for cardiovascular disease. The most significant contributing factor for obesity related dyslipidemia is likely uncontrolled fatty acid release from adipose tissue, especially visceral adipose tissue, through lipolysis, which causes increased delivery of fatty acids to the liver and synthesis of very-low-density lipoprotein (VLDL). Increased levels of free fatty acids can decrease mRNA expression or activity of lipoprotein lipase (LPL) in adipose tissue and skeletal muscle. Increased synthesis of VLDL in the liver can inhibit lipolysis of chylomicrons, which promotes hypertriglyceridemia [231].

Hypercholesterolemia is frequently found in patients with obesity, so that the average serum cholesterol level is significantly higher in overweight subjects than in lean ones, and usually a significant correlation exists between serum cholesterol and obesity [232, 233]. It should be borne in mind, however, that a great many obese patients have normal serum lipid concentrations. Hypercholesterolemia and obesity are known to be associated with the development of ischemic heart disease [234], although the association is relatively weak in the case of obesity, according to recent studies [235, 236]. Results of preliminary studies [252, 253] and those reported here clearly demonstrate that obesity enhances cholesterol synthesis very potently and that reduction of weight effectively normalizes cholesterol production. National institute of health reported that obese individuals are at increased risk of diabetes mellitus, cardiovascular disease, hypertension, and certain cancers, among other conditions [237].

There was very strong correlation between BMI and weight with total cholesterol. High level of total cholesterol in the present study also suggests that obese individuals are at increased risk of hypertension and coronary artery disease. It has been demonstrated by cross-sectional and most of the longitudinal studies that among adults, the total cholesterol level rises as the body mass index rises [238, 239]. Moreover, in the literature there is a widespread opinion that the reduction of BMI will automatically lead to a decrease in cholesterol level [240].

The present study has also revealed a strong association between high levels of cholesterol and obesity. This finding corresponds well with the observations made in other studies such as, for example, the LRC program prevalence study [241], a study from the March 1998 issue

of "Journal of Korean Academic Nursing" found that men and women of various age groups face higher total cholesterol and LDL cholesterol with increased BMIs [242]. Another study from the August 2004 issue of "International Journal of Obesity," consisting of nearly 50,000 subjects of various age groups and ethnicities, found a strong link between high cholesterol and obesity. It's widely speculated that a higher BMI alone is attributable to coronary heart disease [243].

Obesity is a chronic condition that results of an interaction between genetic and environmental factors [244]. Various lipid abnormalities have been observed in obese subjects, including elevated total cholesterol, triglycerides and lower high-density lipoprotein cholesterol levels [245].The dyslipidaemia among the obese subjects might on one hand be due to an increased intake of food rich in saturated fatty acids and cholesterol [234]. On the other hand, to an increased basal cholesterol synthesis and to a decrease in LDL-induced inhibition of endogenous cholesterol synthesis through disturbing activity of 3-hydroxy-3-methylglutarate-coenyzme A [246]. However, the latter was found only in obese subjects with hypercholesterolaemia. In individuals with simple obesity or hypercholesterolaemia, without obesity, alteration of cholesterol synthesis through this pathway was not observed. Moreover, subjects with established obesity have an increased lipogenesis in hepatocytes (not in adipocytes) that might contribute to develop and/or maintain the excessive fat mass and, together with hyperinsulinaemia, might additionally alter lipid homeostasis by promoting cholesterol synthesis. However, the prevalence of high blood cholesterol and mean levels of cholesterol do not increase consistently with increasing BMI above 25 kg/m^2 [247]. In the present analysis we used BMI, which does not describe body fat distribution [238].

Waist circumference is the marker of visceral fat accumulation. The accumulation of visceral fat is particularly assumed to play an important role in the etiology of the diseases. Fatty acids may result from an inability of adipose tissue to sequester fatty acids appropriately for storage [248]. Instead, they are deposited as ectopic fat in skeletal muscle, liver [249], and other organs [250]. It is thought that such fat accumulation is linked to impaired metabolic function of the tissue in question [251, 252]. However, this positive association (in particular with plasma cholesterol) is only present in the upper quartile of the BMI distribution, indicating that obesity is necessary for these relationships to exist [253].

According to the International Diabetes Federation, metabolic syndrome is characterized as the presence of three or more of the following features: obesity, hyperglycemia, hypertension, low high-density lipoprotein (HDL) cholesterol levels, and/or hypertriglyceridemia. Obesity is considered as a pivotal component in metabolic syndrome [254]. Although dysregulated

production of "offensive" adipocytokines in obese patients is strongly associated with metabolic syndrome, recent studies have shown that oxidative stress is also critically involved in the pathogenesis of metabolic syndrome. Oxidative stress is known to impair both insulin secretion by pancreatic β-cells and glucose transport in muscle and adipose tissue. Increased oxidative stress in vascular walls is involved in the pathogenesis of atherosclerosis, hypertension, and hepatic steatosis [255]. Oxidative stress, locally produced in each of the above tissues, induces damage to cell structures, including membranes, proteins and DNA, for these reasons, oxidative stress would appear to be involved in the pathogenesis of each disease leading to metabolic syndrome [253]. Firstly, visceral fat accumulation induces an increase in systemic lipid peroxidation and damage through excess free fatty acid and cytokines like TNF-α, which then triggers systemic oxidative damage [256]. Secondly, patients with metabolic syndrome showed lower anti-oxidant activities. With regard to hypertension, antioxidant and oxidant imbalance is a well-known physiological regulator of arterial pressure, and recent studies noted that oxidative stress causes endothelial dysfunction, leading to increased blood pressure and coronary artery disease. Regarding dyslipidemia, many in vitro and in vivo studies have reported higher ROS release, and lower SOD in dyslipidemia [257].

Considering the strong associations between oxidative stress markers related to oxidative stress, antioxidant status and metabolic syndrome [289] some researchers hypothesized that oxidative stress is an early event and/or a candidate for a pivotal role in the pathology of metabolic syndrome [258]. Moreover, because of enhanced oxidative stress in obesity, the risk of development of metabolic syndrome is even more elevated in overweight or obese subjects [124].

- **Obesity associated oxidative stress: other studies using other biomarkers:**

Evidence of obesity-induced oxidative stress in humans has been accumulating over the past few years. A summary of this evidence is shown in table II.7. The majority of human studies relating obesity and oxidative stress have been cross sectional.

Table II.7: Evidence for obesity-related oxidant stress in humans

Study reference	Subjects	Biomarker	Tissue sample	Major finding
Van Gaal et al. [259]	Pre-menopausal women	TBARS	Plasma non-HDL Lipoprotein	↑TBARS in obese than non-obese women; BMI correlated negatively with lag time
Skrha et al. [260]	Obese, diabetic men and women	MDA	Plasma	↑MDA in obese vs non-obese persons; MDA/SOD ratio was ↓ in obese vs non-obese
Dandona et al. [261]	Obese, non-obese men and women	Protein carbonyls, TBARS	Plasma	↑Protein carbonyl levels and TBARS in obese than non-obese; after caloric restriction biomarkers were ↓ by 87 and 15% of baseline values in the obese group
Block et al. [262]	Men and women	F2-isoprostanes	Plasma	↑Isoprostanes in class II obese than non-obese persons
Davi et al. [263]	Women	8-isoprostanes	Urine	↑ Isoprostane levels in both gynoid and android obese vs non-obese women, with highest levels in the android
Olusi [171]	Children, adults obese, non-obese	MDA	Plasma	↑MDA in obese than non-obese persons; ↓ Erythrocyte CuZn-SOD and GPX values in morbidly obese persons compared with non-obese
Ozata et al. [221]	Men	TBARS	Plasma, Erythrocyte	↑ TBARS and ↓ erythrocyte CuZnSOD and GPX activity in obese than non-obese men
Stojiljkovic et al. [264]	Men and women, hypertensives	F2-isoprostanes	Plasma	Following Intralipid and heparin infusion, plasma F-isoprostane formation ↑more in the obese than the non-obese group

Keaney et al. [265]	Men and women	F2-isoprostanes	Serum	Isoprostane levels ↑ linearly in men and women with BMI > 25 kg/m^2 (for women and men)
Konukoglu et al. [266]	Men and women	TBARS	Plasma	↑ TBARS in obese than non-obese persons
Myara et al. [267]	Men and women	MDA	LDL	↑LDL oxidation lag time in obese than non-obese persons
Russell et al. [268]	Men	4-HNE	Skeletal muscle	↑ 4-HNE in obese than non-obese persons
Urakawa et al. [269]	Men	8-epi PGF2α	Plasma	↑ 8-epi PGF2a in obese than non-obese men; 8-epi PGF2α correlated with fat weight, visceral fat area
Uzun et al. [270]	Men and women, morbidly obese	MDA	ox LDL	↓ MDA in LDL following gastric band surgery
Vincent et al. [271]	Older obese women	PEROX	Plasma	↑Postexercise TBARS and hydroperoxides in obese than non-obese women
Furukawa et al. [124]	Men and women, obese and non-obese	TBARS, 8-epi -PGF2α	Plasma, Urine	↑ TBARS and urinary 8-epi-PGF2α levels were correlated with BMI and waist circumference
Yesilbursa et al. [272]	Men and women, obese	MDA	Plasma	↓MDA following 6 months of orlistat therapy
Ferretti et al. [273]	Obese and non-obese women	PEROX		↑ PEROX in HDL and LDL in obese than non-obese women
Vincent et al. [274]	Men and women, non-obese, obese	PEROX	Plasma	↑Postexercise TBARS and hydroperoxides in obese than non-obese persons

Ozcelik et al. [275]	Men and women, obese	MDA	Serum	Orlistat and exercise training ↓ serum MDA in obese persons compared to Orlistat alone

❖ **Oxidative stress and the paradoxical effects of antioxidants:**

As it has been mentioned in the previous chapter, oxidative stress is referred to imbalance between the reactive oxygen species and antioxidants system to detoxify the reactive intermediates or to repair the resulting damage [276, 277].

Insufficient levels of antioxidants or inhibition of the antioxidant enzymes, cause oxidative stress which may damage all components of the cell, including proteins, lipids and deoxyribonucleic acid [276].

The oxidative stress is thought to be involved in the development of atherosclerosis, heart failure, myocardial infarction, cancer, Parkinson's disease, Alzheimer's disease, sickle cell disease, lichen planus, vitiligo, autism, chronic fatigue syndrome and renal failure [278, 279, 280, 281].

Antioxidants are reducing agents such as thiols, ascorbic acid, or polyphenols molecules that inhibit the oxidation of other molecules by being oxidized themselves [282].

Antioxidants are widely used in dietary supplements and have been investigated for the prevention of diseases such as cancer, coronary heart disease and even altitude sickness. Although initial studies suggested that antioxidant supplements might promote health, later large clinical trials with a limited number of antioxidants detected no benefit and even suggested that excess supplementation with certain putative antioxidants may be harmful [281, 283]. From the literature review it maybe concluded that the diets high in antioxidants (fruits and vegetables) are nearly almost beneficial, but this is not the case for diet supplementations. The possible explanation is that, in the diet, there is a mix of antioxidants and it is well recognized that they work as a continuous chain, while supplementation is usually given using one or two substances. Therefore, the antioxidant chain is not completely available [276, 280].

In this regard, it is well-known that after scavenging free radicals, if an antioxidant is not restored by the following antioxidant in the chain, it begins to be a pro-oxidant. In this situation, the final effect of such supplementations would be no effect or a damaging effect [281, 282].

Therefore, in antioxidant therapy complimentary antioxidants cannot always substitute the fruits and vegetables high in antioxidants [285].

❖ **Exercise-induced oxidative stress in humans:**

Increased production of ROS leading to cellular oxidative stress is linked to numerous pathologies including cancer, diabetes, and neurological diseases [286, 287]. Therefore, it seems paradoxical that although exercise promotes oxidative stress, a routine of regular exercise is associated with numerous health benefits including a lower risk of all-cause mortality, a reduced threat of cardiovascular disease, cancer, and diabetes [288, 289]. The finding that exercise promotes oxidative stress in humans was first reported over 38 years ago [290], when Dillard et al. demonstrated that physical exercise can lead to increased lipid peroxidation. Since this early report, growing evidence indicates that although high levels of ROS production can damage cellular components, low-to-moderate levels of cellular oxidants play important regulatory roles in the modulation of skeletal muscle force production, control of cell signaling pathways, and regulation of gene expression [291, 292].

Many tissues can produce ROS during exercise [292]. However, to date, few studies have investigated which organs are primarily responsible for ROS production in exercising humans because of restricted access to most tissues. The lack of in vivo studies on this topic is due to the difficulty of investigating the multifaceted nature of exercise, which involves several organ systems that are connected through the increased energy requirement of contracting skeletal muscles [292]. Since the discovery that contracting skeletal muscles produce ROS [293], many investigators have assumed that skeletal muscle provides the major source of free radical and ROS generation during exercise [292]. Nonetheless, other tissues such as the heart, lungs, or blood may also contribute to the total body generation of ROS during exercise [292, 294]. For example, phagocytic white cells can play a major role in modifying muscle redox state after exercise-induced muscle damage. Indeed, substantial injury to muscle fibers is accompanied by invasion of the injured area with macrophages and other phagocytic cells [295] and although this process could be essential for effective muscle repair, it also involves the release of substantial amounts of ROS from the phagocytic cells [296].

Characterization of how exercise modulates the immune system in untrained individuals as well as athletes shows how the type, intensity, and duration of exercise affects the immune responses to pathogenic agents, such as bacterial endotoxin LPS [297, 298, 299]. In addition to regular exercise, the ingestion of antioxidant supplements or foods high in antioxidants and vitamins, such as C and E, have become commonplace in efforts to maintain health and prevent chronic oxidative stress associated aliments [300].

While antioxidant supplementation has been shown to alleviate exercise-induced oxidative stress and benefit athletes undergoing long-term strenuous training by reducing oxidative

stress-related injuries and illnesses [301, 302], exercise studies using untrained healthy individuals show that antioxidant supplementation may counteract the healthy benefits of regular exercise [303]. It is therefore possible that the removal of exercise-induced oxidative stress by antioxidant supplementation (and possible anti-inflammatory agents) may also remove any putative enhancement of the innate and adaptive immune system.

Exploring the health properties of fruit and vegetable products during exercise has become the focus of recent research into functional foods. Emerging evidence indicates that fruits contain important flavonoids that underlie both antioxidant [304, 305, 306] and immune modulatory [307] mechanisms that could alleviate oxidative stress as well as enhance innate and adaptive immunity. Although these health benefits are attributed a high antioxidant status, recent feeding and cellular studies indicate that flavonoids and anthocyanins exhibit a range of health benefits, including antioxidant and anti-inflammatory properties [308].

- **Obesity-associated oxidative stress: the chicken or the egg?**

Our study show that in obese subjects, fat accumulation closely correlated with the markers of oxidative stress. But it does not allow for inference causality, it remains to be determined if oxidative stress is a cause or a consequence of obesity.

The theories try to explain the cause and effects of increased oxidative stress in obesity. Nonetheless, a relationship between oxidative stress and obesity is not well understood. It has been reported that obesity may induce systemic oxidative stress and, in turn, oxidative stress is associated with an irregular production of adipokines, which contributes to the development of the metabolic syndrome [309].

Regarding excess oxidation, it is currently believed that excess fat leads to increased oxidation; visceral adipose tissue caused by overconsumption of nutrients plays a central role. As visceral fat stores expand, adipocytes generate increasing levels of ROS that incite increased expression and secretion of inflammatory adipokines [265, 310, 311]. Accumulation of oxidative stress in adipose tissue is one of the early events in the development of metabolic syndrome in obesity [124].

High fat deposition is strictly related to redox unbalance. Juvenile overweight and obesity have been linked to high levels of oxidative stress [312, 313]; a strong significant association, during a five-year follow-up period, was demonstrated by both the Insulin Resistance Atherosclerosis Study (299 participants) [314] and the Health, Aging and Body Composition Study (726 participants) [315]. In mice, diet-induced obesity increases cerebrocortical oxidative stress [316] and high fat diet-induced obesity also correlates with mitochondrial

dysfunction and increased oxidative stress in skeletal muscle and liver [317]. Other research showed that a diet high in fat and carbohydrates induces a significant increase in oxidative stress and inflammation in persons with obesity [318]. On the other hand, weight loss by calorie restriction and/or exercise can ameliorate the state of oxidative stress [319].

Furukawa S et al. [124] observed stimulation of ROS production by fatty acids via NADPH oxidase activation in adipose tissue of obese mice. This in vivo study revealed that oxidative stress increased only in accumulated fat but not in other tissues of obese mice, the mRNA expression levels of NADPH oxidase subunits increased, and mRNA expression levels and activities of antioxidant enzymes decreased [320]. Increased oxidative stress in accumulated fat, via increased NADPH oxidase and decreased antioxidant enzymes, causes dysregulated production of adipocytokines, locally. Increased ROS production from accumulated fat also leads to increased oxidative stress in blood, hazardously affecting other organs including the liver, skeletal muscle, and aorta [124].

Altered antioxidant defenses are also observed in obese people [321], this is not unexpected considering that the different antioxidant enzymes act in a fine-tuned temporal order and at the onset of obesity, tissues try to counteract oxidative stress (induced by elevated circulating fatty acids) by increasing expression and activity of antioxidant enzymes, which are progressively depleted as obesity occurs [322].

Oxidative stress could contribute to obesity in a number of different ways; it might cause an increase in the number of adipocytes, by increasing their rate of production. On the other hand, oxidative stress might change the behavior of adipocytes, by affecting their ability to break down fat for use as fuel.

Youn et al. [323] propose that oxidative stress contributes to obesity rather than the other way around, as has been the conventional thinking (a chicken-and-egg scenario). The most significant finding of their study is the first demonstration that ROS of vascular origin play an important causal role in the development of obesity. They hypothesize that ROS generated in vascular smooth muscle cells by NADPH oxidase induce obesity; this last is a major contributor to oxidative stress in many tissues, including adipose tissue and the vasculature [124, 324, 325]. Conversely, factors causing oxidative stress, such as angiotensin II, that induce insulin resistance do not necessarily induce body weight gain [326]. Therefore, whether oxidative stress, per se, leads to weight gain is an important gap in our understanding of the pathophysiology of obesity.

Epidemiologically, obesity is commonly associated with diseases like hypertension, hypercholesterolemia, and diabetes [327]. Moreover, experimental studies have shown that

these diseases promote vascular ROS production [328]. It has been thought that obesity is often causal in these conditions [329, 330]. Other study suggests that vascular ROS overproduction might instead precede and predispose to the development of obesity and metabolic syndrome. Many obese patients habitually consume a high-fat diet. Youn et al. [323] suggest that coexisting conditions associated with increased vascular ROS production, such as hypertension or hypercholesterolemia, might serve as a second stimulus in addition to dietary indiscretion, together contributing to development of obesity and metabolic syndrome.

- **Keeping the balance: health and lifestyle**

The results found in this study suggest that in obese individuals there is an increase level of oxidative stress comparing to the non-obese individuals by depletion in antioxidants, which means that there is a relationship between obesity and oxidative stress. These results lead us to confirm that obese people should prevent their oxidative stress by having an antioxidant-rich diet. That doesn't mean that persons with normal BMI shouldn't take care of their alimentation and having a healthy life style

Strategies designed to increase antioxidant defenses in obese subjects could be useful to prevent and treat obesity co-morbidities. Obesity-associated oxidative stress and diseases can be reduced mainly by weight loss together with physical activity; Combination of hypoenergetic diet with regular moderate aerobic exercise potentiates the beneficial effects on redox balance. Regular physical activity appears to act as a natural antioxidant and anti-inflammatory strategy for preventing obesity-associated complications. Therefore, this should be the first and more important goal to be achieved. Secondly, obese subjects should obtain a great benefit from a regular consumption of foods exerting positive effects on health, studies have shown that antioxidants supplements do not replicate the action of antioxidants from food, such as fruits and vegetables (rich in antioxidant vitamins, phytochemicals, and fiber), tea (rich in cathechins), spices (such as curcumin and red hot pepper) and fish (rich in ω-3). Some dietary components such as fat dairy products, sugar-rich soft drinks and diet rich in saturated fatty acids deeply contribute to oxidative stress; thereby reducing their content in food may be helpful to improve redox state, independently from weight reduction. Dietary factors have been shown to promote fat deposition and regain weight following weight loss.

5. Conclusion:

Summarizing our data by multidimensional statistical analysis, we can draw the conclusion that obesity is a state of chronic oxidative stress. High levels of cooper/zinc ratio together with the low antioxidant capacity detected in the case of obese patients indicate elevation of oxidative stress. This imbalance in prooxidant/antioxidant status may result in a higher risk of atherosclerotic and diabetic complications in obese adults.

These markers of oxidative stress can be used either as markers of following the success of different treatment modalities or considering the role of antioxidant treatment in obesity.

Since obesity is considered to be influenced by many factors, implementation of extensive forthcoming studies with more and new parameters will contribute to our study with wide perspective, future surveys and epidemiologic studies should measure at least more markers of oxidative damage, as well as superoxide dismutase, glutathione peroxidase, glutathione reductase and total antioxidant status. These data would permit a better understanding of the role that oxidants and antioxidants play in the health of human populations. Very few studies conducted in Algeria to evaluate the association between oxidative stress and obesity, even though a small number of samples were used in our study, this results should not be overlooked as it may form the basis for future research.

This study demonstrated that in obese subjects, fat accumulation closely correlated with the markers of oxidative stress. But it does not allow for inference causality, it remains to be determined if oxidative stress is a cause or a consequence of obesity.

In conclusion, oxidative stress may be the mechanistic link between obesity and diseases. Strategies designed to increase antioxidant defenses in obese subjects could be useful to prevent and treat obesity co-morbidities. Obesity-associated oxidative stress can be reduced mainly by weight loss together with physical activity; therefore, this should be the first and more important goal to be achieved. Secondly, obese subjects should obtain a great benefit from a regular consumption of foods exerting positive effects on health, antioxidant supplementation should be useful to prevent or slow down progression of associated pathologies.

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Abstract
Obesity has become a leading global health problem owing to its strong association with a high incidence of diseases including diabetes, cardiovascular disease, non-alcoholic fatty liver disease, and cancer. It is often accompanied by an increased risk of mortality and, in the case of non-fatal health problems, the quality of life is impaired because of associated conditions, including sleep apnea, respiratory problems, osteoarthritis, and infertility. Oxidative stress has been considered one of the mechanisms linking obesity to related complications.
The oxidative stress parameters are compared in obese subjects matched healthy controls. Our aim was to determine the relationship between obesity and oxidative stress. The present study focused on a sample of 60 volunteers (17 men and 43 women), aged 18-62 years of both genders in the city of Tlemcen, divided according to their BMI into two groups: non obese group (BMI <25 kg/m^2) and obese group (BMI ≥ 30 kg/m^2).
The status of oxidative stress was evaluated by determining the serum levels of vitamin C, copper and zinc. The study revealed that copper to zinc ratio was significantly higher in obese subjects compared with those having normal BMI (*P <0.05*), vitamin C and zinc concentrations were significantly lower in obese versus non obese subjects. The decrease in antioxidant defenses and increased copper to zinc ratio in obese subjects reflect a profound oxidative stress, which would be one of the mechanisms involved in the onset of diseases caused by the obesity.

Keywords: obesity; oxidative stress; vitamin C; zinc; copper to zinc ratio.

ملخص
أصبحت السمنة مشكلة صحية عالمية رائدة نظرا لارتباطها القوي مع وجود نسبة عالية من الأمراض بما في ذلك السكري وأمراض القلب والأوعية الدموية، مرض الكبد الدهني، والسرطان وغالبا ما يصاحب ذلك زيادة خطر الوفاة، وقد تكون مشاكل صحية غير مميتة بما في ذلك توقف التنفس أثناء النوم، مشاكل في الجهاز التنفسي، التهاب المفاصل، والعقم. وقد اعتبرت الأكسدة واحدة من الآليات التي تربط بين السمنة و مختلف الأمراض.
لتحديد العلاقة بين السمنة والأكسدة. أجرينا هذه الدراسة على عينة من 60 متطوعا (17 رجلا و 43 امرأة)، تتراوح أعمارهم بين 18-62 عاما في مدينة تلمسان، وتنقسم وفقا لمؤشر كتلة الجسم إلى مجموعتين: المجموعة الأولى تتكون من أشخاص دوي وزن طبيعي (مؤشر كتلة الجسم < 25) و المجموعة الثانية تتكون من أشخاص يعانون من السمنة (مؤشر كتلة الجسم ≤30).
تم تقييم حالة الأكسدة من خلال تحديد مستويات الفيتامين ج في المصل إضافة إلى النحاس والزنك. وكشفت الدراسة أن نسبة النحاس / الزنك أعلى بكثير لدى الأشخاص اللذين يعانون من السمنة مقارنة مع دوي الوزن الطبيعي أما قيمة الفيتامين ج والزنك فكانت منخفضة لدى الأشخاص اللذين يعانون من السمنة مقارنة مع المجموعة الأخرى.
انخفاض مضادات الأكسدة وزيادة نسبة النحاس / الزنك لدى البدناء يبين وجود أكسدة، والتي ستكون واحدة من الآليات التي تشارك في ظهور الأمراض الناجمة عن السمنة.

الكلمات المفتاحية : السمنة; الاكسدة; فيتامين ج; الزنك; النحاس/الزنك.

Résumé
Au centre de tout le métabolisme énergétique, la signalisation des radicaux libres est un élément d'une extrême importance. Ainsi de nombreuses pathologies, impliquant le stress oxydant dans leur développement, ont été recensées. Outre les maladies cardio-vasculaires (oxydation des lipides) et le cancer (oxydation de l'ADN), c'est certainement dans le cadre du diabète (obésité, syndrome métabolique) que des avancées spectaculaires ont récemment été réalisées.
L'objectif de cette étude est de déterminer la relation entre l'obésité et le stress oxydant. Cette étude a porté sur un échantillon de 60 volontaires (17 hommes et 43 femmes), âgés de 18-62 ans dans la ville de Tlemcen, répartis en fonction de leur IMC en deux groupes: le groupe des non obèses (IMC <25) et le groupe des obèses (IMC ≥ 30).
L'état de stress oxydant a été évalué en déterminant la concentration de la vitamine C, le cuivre et le zinc sériques. L'étude a révélé que le rapport cuivre/zinc était significativement plus élevé chez les sujets obèses par rapport à ceux ayant un IMC normal (*P <0.05*), les concentrations de la vitamine C et de zinc étaient significativement plus faibles chez les obèses par rapport aux sujets non obèses. La diminution des défenses anti-oxydantes et l'augmentation de rapport cuivre/zinc chez les sujets obèses reflètent un stress oxydatif profond, ce qui serait l'un des mécanismes impliqués dans l'apparition des maladies provoquées par l'obésité.

Mots clés: obésité; stress oxydant; dosage du zinc sérique; le ratio cuivre/zinc; vitamine C.