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Obesity and Oxidative Stress

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Abstract – Obesity is a chronic metabolic disorder marked by the excessive accumulation of body fat, presenting a significant threat to overall health. This review aims to provide a comprehensive examination of obesity by investigating its underlying causes, associated comorbidities, and treatment options. Additionally, it explores the complex relationship between obesity and oxidative stress, focusing on how obesity affects oxidative stress markers and the subsequent impact on health outcomes. The review begins with an analysis of the primary causes of obesity, which include genetic predispositions, environmental factors, behavioral patterns, and socioeconomic influences. These factors contribute to the development and persistence of obesity by affecting energy balance, fat storage, and metabolic processes. Understanding the connection between oxidative stress and obesity takes up a large amount of the review. The pathophysiology of obesity heavily relies on oxidative stress, which is defined as an imbalance between antioxidant defenses and reactive oxygen and nitrogen species (ROS/RNS). We examine how increased adiposity influences oxidative stress markers, leading to cellular oxidative damage, inflammation, and metabolic dysfunction. In conclusion, this review offers a thorough analysis of obesity, emphasizing its causes, associated health issues, and the intricate relationship between obesity and oxidative stress.

Keywords – Obesity, Oxidative Stress.

I. INTRODUCTION

Obesity represents a complex and multifactorial condition, defined by an excessive accumulation of body fat that poses significant risks to overall health. This condition is typically evaluated using the Body Mass Index (BMI), a metric derived by dividing an individual's weight in kilograms by the square of their height in meters (kg/m^2). According to established guidelines [1], a BMI of $30 \text{ kg}/\text{m}^2$ or higher is classified as obesity. The etiology of obesity is intricate, involving an interplay of various factors including genetic predisposition, environmental influences, behavioral patterns, and socioeconomic conditions. Genetic predispositions may determine how the body metabolizes and stores fat, while environmental factors, such as the availability of high-calorie foods and the prevalence of sedentary lifestyles, greatly influence the risk of developing obesity. Behavioral habits, particularly unhealthy eating patterns and insufficient physical activity, further exacerbate this risk. Moreover, psychological factors, including stress and emotional eating, alongside socioeconomic disparities, play pivotal roles in not only increasing the likelihood of obesity but also in hindering effective weight management [2,3]. Addressing obesity requires a comprehensive, multifaceted strategy. Effective intervention involves more than just curbing sedentary behaviors; it necessitates a holistic approach that includes dietary modifications, increased physical activity, and behavioral therapies aimed at sustainable lifestyle changes. In cases where lifestyle modifications are insufficient, medical interventions such as pharmacotherapy or bariatric surgery may be warranted [4]. Recognized as a chronic disease, obesity leads to profound physiological,

anatomical, and metabolic alterations, which can adversely affect an individual's overall health [5,6]. It is well-documented that being overweight or obese substantially elevates the risk of premature mortality when compared to being underweight. Globally, the prevalence of obesity has surged to alarming levels, now surpassing the incidence of underweight in most regions, with the exception of certain areas in sub-Saharan Africa and Asia [7]. This global trend contributes to higher mortality rates across all age groups, reinforcing the urgent need for effective public health strategies. BMI, as a measure, not only indicates the degree of obesity but also reflects body fat percentage, which can vary depending on factors such as sex, age, and ethnicity [8]. Historical data, such as those from the second National Health and Nutrition Examination Survey in the United States, identified specific obesity thresholds—a BMI of 27.8 kg/m² or higher for men and 27.3 kg/m² or higher for women [9]. These findings highlight the critical importance of addressing obesity as a major public health challenge. To effectively combat obesity, it is essential to understand its multifaceted nature and the complex interaction between various risk factors. A multi-pronged approach, encompassing lifestyle changes, medical interventions, and ongoing research, is crucial in tackling both the underlying causes and the subsequent health consequences of obesity. By focusing on comprehensive management strategies, significant improvements in public health outcomes can be achieved, thereby mitigating the growing burden of obesity-related diseases on healthcare systems worldwide.

II. CAUSES

Obesity emerges as a result of the body's excessive accumulation of fat, which occurs due to a persistent imbalance between the energy consumed and the energy expended. Specifically, obesity develops when an individual's caloric intake consistently exceeds their energy expenditure over an extended period, leading to the abnormal storage of fat within the body's adipose tissues [6]. This imbalance, primarily driven by a significant surplus of calories, results in the conversion and deposition of excess energy as fat in adipose cells. As these fat cells continue to expand abnormally, they disrupt the intricate network of nutritional signals and metabolic processes that are responsible for maintaining a healthy body weight, further accelerating the development of obesity [10]. The dysfunction in these metabolic pathways not only exacerbates fat accumulation but also contributes to the systemic inflammation and insulin resistance often associated with obesity [11]. Genetic predisposition and a family history of obesity are critical determinants of an individual's susceptibility to becoming overweight or obese. These genetic factors, combined with familial patterns of behavior and lifestyle, create a predisposition for the body to store fat more readily [11]. The interaction between genetic inheritance and environmental factors plays a pivotal role in influencing how the body manages energy storage and utilization, often tipping the balance in favor of fat accumulation. In addition to genetic factors, lifestyle choices are instrumental in the development and progression of obesity. Sedentary behaviors, poor dietary habits, and insufficient physical activity are among the most significant contributors to an increased risk of obesity [13]. These lifestyle factors, when coupled with modern conveniences that promote inactivity and the consumption of calorie-dense foods, create a perfect storm for weight gain. Urbanization introduces a unique set of challenges that further compound the risk of obesity. The rapid pace of life, increased stress levels, and the prevalence of unhealthy food options in urban settings often lead to weight gain. The lifestyle changes associated with urban living, such as reduced opportunities for physical activity and greater access to high-calorie, processed foods, can exacerbate the tendency to gain weight [14,15]. Furthermore, urban environments may foster social and economic pressures that contribute to unhealthy eating patterns and reduced physical activity, thereby increasing the risk of obesity. Moreover, certain medical conditions are known to predispose individuals to obesity, complicating the overall management of their health. Conditions such as polycystic ovarian syndrome (PCOS), hypothyroidism, Cushing's Syndrome, and Prader-Willi Syndrome (PWS) not only elevate the risk of obesity but also present additional challenges for maintaining a healthy weight. These conditions interfere with hormonal and metabolic pathways in ways that make weight management particularly difficult [16]. For instance, PCOS is associated with insulin resistance and hormonal imbalances that contribute to weight gain, while

hypothyroidism can slow metabolism, leading to an increase in body weight. Similarly, Cushing's Syndrome is characterized by excessive cortisol production, which promotes fat accumulation, particularly in the abdominal region, and Prader-Willi Syndrome is a genetic disorder that results in chronic feelings of hunger and a propensity for obesity [11-17]. Addressing obesity requires a holistic and multifaceted approach that takes into account the complex interplay between genetic predispositions, environmental factors, lifestyle choices, and the impact of specific medical conditions. Understanding these diverse influences is essential for developing effective strategies for the prevention, management, and treatment of obesity. By tailoring interventions to address the unique challenges faced by individuals at risk for or already suffering from obesity, healthcare providers can better support long-term weight management and improve overall health outcomes. The need for comprehensive strategies that integrate behavioral, medical, and societal interventions is critical in the fight against the obesity epidemic, as these approaches offer the best hope for curbing its prevalence and mitigating its associated health risks [10-17].

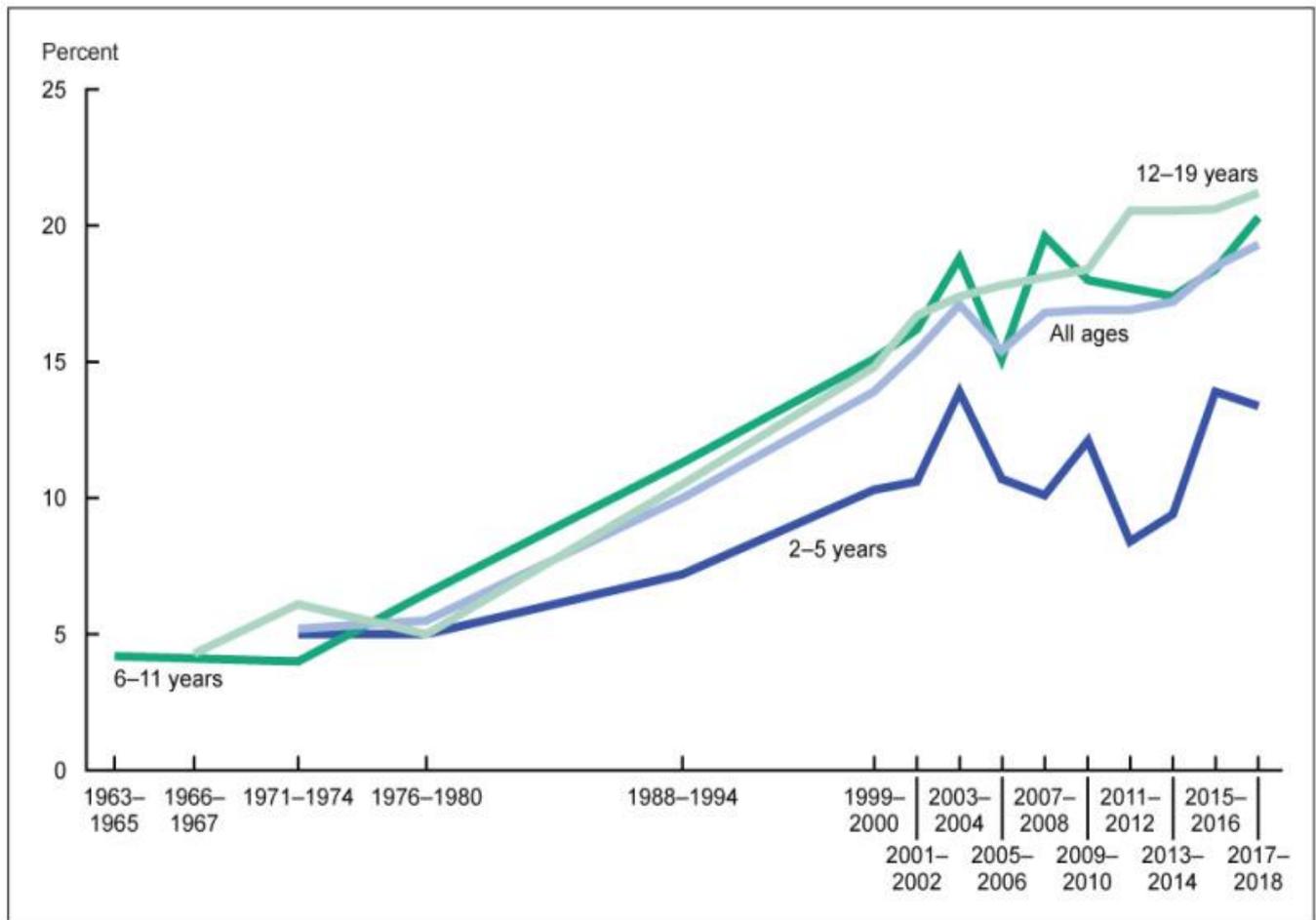
III. ETIOLOGY

Obesity develops from an energy imbalance where the intake of calories consistently surpasses the amount of energy expended, leading to the accumulation of surplus energy in the body's adipose tissue. This excess energy is stored as fat, causing fat cells to expand abnormally, which in turn disrupts the normal signaling pathways that regulate body weight and contribute to the pathological development of obesity [13]. Among the various forms of obesity, abdominal obesity, which is characterized by the accumulation of fat in the abdominal region, is particularly concerning due to its strong association with increased health risks and complications [17]. The accumulation of visceral fat in the abdomen is linked to a higher likelihood of developing a wide range of serious health conditions. Obesity is associated with a multitude of health issues, many of which are life-threatening. It is a significant risk factor for the development of various types of cancer, including but not limited to breast, prostate, ovarian, endometrial, colorectal, esophageal, kidney, and pancreatic cancers. The presence of obesity also elevates the risk of developing chronic conditions such as type 2 diabetes, stroke, hypertension, coronary artery disease, congestive heart failure, asthma, chronic back pain, pulmonary embolism, osteoarthritis, and gallbladder disease. These health complications collectively contribute to the elevated mortality rates observed in obese populations worldwide [18]. The impact of obesity on public health is profound and far-reaching. It not only significantly reduces life expectancy but also places a substantial burden on healthcare systems across the globe. The management and treatment of obesity-related conditions require extensive healthcare resources, leading to increased medical expenses and higher rates of healthcare utilization. Beyond its physical health implications, obesity is also intricately connected to a range of chronic medical conditions that impair an individual's quality of life [19]. These conditions not only diminish physical health but also lead to psychological and social challenges. Recent research has shed light on the broader implications of obesity, highlighting its association with various psychological and social difficulties. Individuals suffering from obesity often experience a range of mental health issues, including mood disorders, low self-esteem, and motivational problems. They may also face challenges related to eating behaviors and interpersonal communication, all of which can negatively impact their overall quality of life [11]. The psychosocial effects of obesity are extensive and complex, encompassing an increased susceptibility to mental health conditions such as depression and anxiety. Additionally, obesity can lead to problematic peer relationships, reduced self-confidence, distorted body image, and disordered eating behaviors. These psychosocial issues are often exacerbated by factors such as age and gender, which serve as additional risk factors for the development of social and psychological disorders [20]. For instance, younger individuals or those of a particular gender may face heightened pressures related to body image, leading to more severe psychological impacts. Given the multifaceted nature of obesity, it is clear that addressing this condition requires a comprehensive and holistic approach. This approach must not only focus on physical health but also consider the psychological and social dimensions of obesity in order to improve overall well-being and quality of life. Effective interventions should aim to address the

root causes of obesity while also providing support for the mental and emotional challenges that often accompany this condition. By taking into account the full spectrum of issues associated with obesity, healthcare providers can develop more effective strategies for prevention, management, and treatment, ultimately leading to better health outcomes for those affected by this condition [11-20].

IV. EPIDEMIOLOGY

The rate of extra weight gain has doubled worldwide since 1980 [21], and the obesity percentage has increased in both men and women of all ages, with a higher rate in women and older persons [22]. Obesity in childhood and adulthood from 2–19 years, by age: the United States, 1963–1965 through 2017–2018 [22]. Figure 1 shows obesity in childhood and adulthood.



NOTE: Obesity is body mass index (BMI) at or above the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts. SOURCES: National Center for Health Statistics, National Health Examination Surveys II (ages 6–11), III (ages 12–17); and National Health and Nutrition Examination Surveys (NHANES) I–III, and NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018.

Fig. 1. Age-specific rates of childhood and adult obesity, from 1963–1965 to 2017–2018 in the United States [23].

V. TREATMENT OF OBESITY

When an individual's Body Mass Index (BMI) exceeds 40, or is above 35 accompanied by a significant inability to lose weight through lifestyle modifications or medical interventions, bariatric surgery becomes a viable and effective solution for weight management [24]. Bariatric surgery is particularly significant due to its multifaceted benefits, which extend beyond mere weight loss. It plays a crucial role in mitigating obesity-related chronic inflammation, which is a key factor in the development of many comorbidities associated with obesity. Additionally, bariatric surgery has been shown to induce favorable changes in the gut microbiota, the diverse community of microorganisms residing in the digestive tract. These alterations in the gut microbiota contribute to improved metabolic health and can lead to long-term

remission of type 2 diabetes and normalization of related biomarkers [25]. An emerging and innovative approach in the treatment of obesity is Faecal Microbiota Transplantation (FMT). This technique involves the transfer of gut microbes from a healthy, non-obese donor to an obese patient. The underlying premise of FMT is that the gut microbiota plays a significant role in energy metabolism and fat storage, and that by altering the microbial composition in the gut, it may be possible to influence the patient's weight and metabolic health. In cases where obese patients have successfully lost weight and maintained their weight loss during the initial phases of treatment, FMT presents a promising method for further modifying obesogenic (obesity-promoting) microbial families within the gut [26]. This intervention could potentially support sustained weight loss and prevent weight regain by promoting a more favorable microbial environment that is less conducive to fat accumulation. Table 1 provides an overview of various weight loss methods and their underlying mechanisms, highlighting the range of strategies available for managing obesity. The integration of surgical interventions like bariatric surgery with emerging therapies such as FMT underscores the importance of a comprehensive approach to obesity treatment. By addressing both the physiological and microbial factors that contribute to obesity, these methods offer hope for more effective and sustained weight management in individuals who struggle with this condition.

Table 1. Comparison of Common Weight-Loss Medications and Their Mechanisms

| Weight-loss medication | How it works | References |
|--|--|------------|
| Orlistat (Xenical) is Available in lower doses without prescription OTC. | Act in the gut to decrease the amount of fat absorbed from food. | [27] |
| Liraglutide (Saxenda) only as an injection. | It may reduce hunger or elevate feelings of satiation. | [28] |
| Naltrexone-Bupropion (Contrave). | A mix of these drugs, naltrexone and bupropion, decreases hunger or increases the feeling of satiation. | [29] |
| (Qsymia) Phentermine-Topiramate. | This drug combines topiramate, which treats migraine headaches, with phentermine, which decreases appetite. This increases the feeling of satiation and decreases the feeling of hunger. | [30] |
| Gelesis (Plenity) | The pieces of gel elevate the elasticity and the volume of the small intestine and the stomach contents, | [31] |

| | | |
|--|--|------|
| Setmelanotide (Imcivree) | This drug acts as an agonist of the MC4R, used in severe obesity because of deficiency of either POMC, PCSK1, or LEPR. | [32] |
| Other medications that decrease your portability to eat include Phentermine (Adipex, Suprenza), benzophetamine (Regimex, Didrex), diethylpropion (Tenuate), and Phendimetrazine (Bontril PDM). | Elevate the rate of some chemicals in the brain that decrease the hunger feelings or increase the satiation feelings. | [33] |

Obesity is becoming a world health issue, and the best solution to prevent and manage this issue is a team of surgeons, a bariatric nurse, an endocrinologist internist, a primary care provider, and a pharmacist [34–36]. This team is called an inter-professional team. Often, all obesity treatments have potential adverse effects and limitations. So, we should educate the patient about the importance of a lifestyle change. Even if a patient has surgery, many programming exercises are essential in preventing weight gain after surgery. Until now, there is no magic treatment for obesity. All techniques and treatments have significant failure levels, and the surgery has life-threatening complications and minions [34,35].

The most crucial behaviour and technique to decrease the level of obesity is the coordination between the schools, the fast-food industry, dietitians, clinicians, physical therapists, using functional foods and public health authorities to make the best and safest habits of eating [34,35,37]. The change in Lifestyle alone can give solutions for obese people to reverse their weight gain, but the big issue is that a lot of people are not motivated to move, do sports, and exercise [34,35,38].

VI. OXIDATIVE STRESS

Oxidative stress is defined by an imbalance between reactive oxygen and nitrogen species (ROS/RNS) and the body's antioxidant defenses [39, 40]. This condition arises when there is an excess of ROS/RNS due to a reduction in cellular antioxidants [39, 41]. The interplay between oxidative stress and obesity is particularly noteworthy because oxidative stress is a significant contributor to the onset and progression of obesity and its associated risk factors [42]. Research has consistently highlighted the detrimental impact of oxidative stress on obesity, demonstrating its role in exacerbating this condition and its related complications [43]. Obesity poses a serious health challenge globally, affecting both developed and developing countries. It significantly increases the risk of numerous health issues, contributing to higher morbidity and mortality rates across all demographics, including various age groups and genders [44]. To combat obesity effectively, it is crucial to engage in regular physical activity, consume a diet rich in antioxidants, vegetables, and polyunsaturated fats, and reduce intake of high-calorie foods. These measures can substantially diminish both the prevalence and severity of obesity [45]. The correlation between rising obesity rates and increased mortality is well-documented. According to [46], obesity and overweight are linked to approximately 280,000 to 325,000 deaths annually in the United States. Notably, more than 80% of these deaths occur among individuals with a BMI exceeding 30 kg/m². Additionally, the Centers for Disease Control and Prevention (CDC) reports that the combination of unhealthy lifestyle choices and poor dietary habits could result in an extra 400,000 deaths per year. This makes lifestyle factors the second leading cause of death in the U.S., following smoking [47]. The Aerobics Center Longitudinal Study, which monitored 25,714 men over a span of 1 to 10 years, reveals that men with a BMI exceeding 30 kg/m² face higher rates of cardiovascular and overall mortality. Conversely, those with a BMI between 18.5 and 24.9 kg/m²

exhibited the lowest mortality rates. Men falling in the BMI range of 25 to 29.9 kg/m² had mortality rates that were intermediate between these two extremes [48]. This underscores the substantial health risks linked to elevated BMI and highlights the need for comprehensive obesity management strategies, including lifestyle changes and preventive actions. In the same cohort, cardiovascular-related mortality increased from just over five deaths per 10,000 person-years among those with body fat percentages below 16.7% to nearly eight deaths per 10,000 person-years for individuals with body fat percentages ranging from 16.7% to 25.0%. For those with body fat percentages exceeding 25.0%, the rate rose to almost 12 deaths per 10,000 person-years [48]. Similarly, the Nurses' Health Study identified a gradual increase in mortality risk for women with a BMI over 29 kg/m², with the lowest mortality rates found in women who weighed at least 15% below the national average for their age group and those whose weight had remained stable since early adulthood [48]. The American Cancer Society's Cancer Prevention Study, which tracked 62,116 white men and 262,019 white women for 14 years, also found that high BMI is associated with elevated mortality rates from all causes, including cardiovascular disease, up to the age of 75. The impact of excess body weight was notably more significant among younger individuals compared to older adults [49]. The aetiology of obesity is multifactorial, encompassing environmental, social, genetic, and hormonal factors [50]. Furthermore, oxidative stress plays a crucial role in the development of obesity. It contributes to the accumulation of white adipose tissue (WAT) by accelerating the proliferation of preadipocytes, promoting the differentiation of adipocytes, and enlarging mature adipocytes. Additionally, oxidative stress exacerbates the health issues associated with obesity, with a positive correlation observed between BMI and oxidative stress biomarkers [51,52]. Interestingly, research has shown that the activity of antioxidant enzymes in the erythrocytes of obese individuals tends to be lower compared to those in healthy subjects [53,54]. This finding highlights a significant aspect of oxidative stress in obesity. The pioneering "TEKHARF " conducted in Turkey was among the first to link excess adipose tissue in obesity with increased production of reactive oxygen species (ROS) through various mechanisms such as mitochondrial dysfunction and inflammatory processes [55]. High levels of fat deposition are strongly associated with a redox imbalance, which contributes to oxidative stress. This imbalance is particularly notable in obese and overweight juveniles, where elevated oxidative stress levels are commonly observed [56]. These oxidative stress markers do not function as prognostic markers for the onset of obesity, despite a strong association between oxidative stress and obesity. Instead, they highlight the increased prevalence of metabolic and cardiovascular disorders among obese and overweight individuals. Specifically, oxidative stress markers have been linked to conditions such as hyperglycemia, hyperlipidemia, and systemic inflammation. In younger populations who are obese or overweight, there is a positive correlation between advanced oxidation protein products (AOPPs) and metrics such as central adiposity, triglycerides, and insulin levels. Conversely, these markers show a negative correlation with the glucose-to-insulin ratio and HDL cholesterol, indicating a higher metabolic risk [57,58]. Despite these correlations, the precise relationship between body mass index (BMI), body fat percentage, and antioxidant defenses remains unclear [59]. The progression of obesity involves the body's response to oxidative stress by upregulating the expression and activity of antioxidant enzymes. This adaptation reflects the body's attempt to counteract oxidative damage. Furthermore, alterations in antioxidant defenses among obese individuals underscore the complex interplay between oxidative stress and obesity, necessitating further research to clarify these interactions and their implications for health.

VII. CONCLUSION

In conclusion, the intricate relationship between oxidative stress and obesity underscores the multifaceted nature of this global health challenge. Obesity, a condition that affects both developed and developing nations, significantly contributes to elevated morbidity and mortality across various age groups and genders. This condition not only leads to an increased prevalence of chronic diseases but also strains healthcare systems worldwide. Evidence from numerous studies indicates that oxidative stress plays a critical role in the onset and progression of obesity. It is associated with various metabolic

and cardiovascular diseases, exacerbating the health impacts of obesity. When this balance is disrupted, it leads to cellular damage, inflammation, and promotes the proliferation of adipocytes (fat cells) and the accumulation of white adipose tissue. These processes are pivotal in the development of obesity and its associated complications. Research highlights that oxidative stress not only contributes to the initial development of obesity but also perpetuates its progression. The excess ROS generated during oxidative stress can impair insulin signaling, increase inflammation, and disrupt metabolic pathways, thereby exacerbating obesity-related health issues. To address the obesity epidemic effectively, it is essential to implement preventive measures that target both oxidative stress and obesity directly. Increasing physical activity and making dietary modifications, particularly enhancing antioxidant intake through fruits, vegetables, and other nutrient-rich foods, are crucial steps. These interventions can help counteract the oxidative damage and improve metabolic health. Furthermore, understanding the complex interactions between oxidative stress and various factors—such as genetic predispositions, environmental exposures, and lifestyle choices—is vital for developing comprehensive strategies to combat obesity. Research must continue to explore the exact mechanisms through which oxidative stress influences obesity and to identify effective interventions. This includes studying how different antioxidants, lifestyle changes, and medical treatments can mitigate oxidative stress and its effects on obesity. Overall, a multifaceted approach that combines lifestyle modifications, dietary changes, and continued scientific research is necessary to address both the causes and consequences of obesity. By fostering collaboration among researchers, healthcare providers, and policymakers, significant progress can be made in improving health outcomes, reducing the prevalence of obesity, and alleviating the associated public health burden. Through concerted efforts, we can work towards a healthier future, marked by reduced rates of obesity and its related diseases, and an enhanced quality of life for individuals worldwide.

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