OBESITY AND OXIDATIVE STRESS: IS THERE A LINK?

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Abstract

Obesity is the pandemic of the new world. The abundance of literature on obesity still does not clearly explain the pathophysiological mechanism of obesity related comorbidities. Oxidative stress is an imbalance between the reactive oxygen species and the antioxidant system of the body. Oxidative stress may be the bridging link between obesity and its associated comorbidities. Research suggests the correlation between the two but still ambiguity looms over due to the BMI cut-offs considered for obesity in various ethnicities and the heterogenicity of biomarkers of oxidative stress in obesity. This narrative review aims to summarize the current knowledge of oxidative stress in relation to various grades of obesity.

1. INTRODUCTION

Obesity is a worldwide prevalent health issue. Increase in body mass and an imbalance in energy consumed and energy utilized are characteristics of obesity (1). Obesity results in excessive fat accumulation and is suggested to be a predisposing risk factor in progression of several diseases like Hypertension, Type II diabetes, Cancer, Depression etc. (2). Body Mass Index (BMI) forms the basis to classify obesity. BMI is given by weight in kilograms divided by the height in meters square. WHO defines 18.5 kg/m^2 to 24.9 kg/m^2 as normal BMI, whereas a BMI ≥ 25 kg/m^2 falls in the overweight category and BMI ≥ 30 kg/m^2 is considered as obese. Severe obesity is defined as BMI ≥ 40 kg/m^2 (1). For Asian populations, a BMI of 27.5 kg/m2 or more is considered obese whereas a BMI over 23 kg/m2 is an index of being overweight (3). The Obesity epidemic is becoming the major cause of morbidity in middle- and low-income countries increasing the economic burden of the disease. When body weight goes up by 1 standard deviation, mortality goes up by 30%, and when fat content goes down by 1 standard deviation, mortality goes down by 15%. (4). The Adipose tissue, secretes biologically active molecules like adipocytokines or adipokines and is considered as an active endocrine organ (5). Chronic low grade inflammation with increased oxidative stress (OS) as seen in Obesity, is attributed to complex interplay between these adipokines (5**).** Oxidative stress (OS) is described as a state in which there is an imbalance between the ROS (Reactive Oxygen Species) and cellular antioxidants in the body with Reactive Oxygen Species overriding the antioxidant system. (6). Reactive oxygen species (ROS) are formed physiologically in the body and their excess causes the oxidative degradation of lipids, a known cause of cellular injury (7)**.**Oxidative stress is considered to be one of the molecular mechanisms involved in complications associated with obesity. Obese people exhibit higher levels of oxidative stress indicators (8) and lower levels of antioxidant enzymes, indicating a weakened antioxidant defence system against oxidative stress (OS) (9). Since oxidative stress plays a crucial role in the accumulation of adipose tissue, preadipocyte proliferation, and adipocyte differentiation and growth, there is a cause-and-effect relationship between oxidative stress and obesity. (10).

Over the last few decades transitions in nutritional, demographic and socioeconomic conditions in developing nations has resulted in increased prevalence of obesity. The Overweight /Obesity prevalence in India has been estimated as 38.4% and 36.2% in men and women respectively (11) and this is expected to increase considerably by 2040 (12). There is plethora of literature defining the role of obesity as a risk factor in several diseases (13) still, the exact mechanism of the link between obesity and pathogenesis of a disease has not been illustrated in depth. Oxidative stress markers may explain this missing link.

Increased incidence of Cardio Vascular Disease (CVDs) particularly among young in past two decades, may be associated with increased incidence of obesity (14). Several researches have highlighted the role of oxidative stress in obesity and more studies are needed to establish the exact role (OS) plays in obesity complications. The estimation of oxidative stress can be considered as a marker for predicting development of metabolic diseases related to obesity, and this knowledge can be put to clinical use for intervention at an early stage of disease.

2. RESEARCH QUESTION

Is obesity a state of increased oxidative stress in the body and what are the levels of markers of oxidative stress (OS) and antioxidants, in relation to various grades of Obesity?

3. LITERATURE SEARCH

The literature search was conducted in the PubMed and Web of Science electronic databases from May 2023' to June 2023'. The search was limited to publications from the last 7 years (2019–2023), so as to present the current state of research. Only English-language publications were included. Search terms were limited to titles and abstracts and full text and based on all possible combinations of the following keywords: "Obesity", Body Mass Index AND "oxidative stress" OR "redox" AND "lifestyle intervention" OR "lifestyle Intervention" , "Obesity" AND Oxidative stress.

3.1 Eligibility Criteria

Studies that assessed the levels of biomarkers of oxidative stress in various grades of obesity and in various age groups were included in the review.

The inclusion criteria were:

- Articles that measured at least one of the following oxidative stress parameters: GSH (Glutathione), SOD (Superoxide dismutase), CAT (Catalase), and lipid peroxidation product MDA (Malondialdehyde) or Antioxidants - Vit C, Vit E , Total Antioxidant Capacity. (TAC)
- Observational studies (cross-sectional, longitudinal, case control, or cohort studies) and Interventional studies.

The exclusion criteria were:

- Any Research which was not an original article (e.g., review articles, editorials).
- Studies whose full text was not published in English.
- Animal studies

4. RESULTS

The studies Selected summarizing the levels of oxidative markers in obese subject are listed in the Table 1.

Table 1: Summary of Studies on the Relationship between Obesity and Oxidative Stress Biomarkers

Author, year	Study Sample	Study group	Control group	Biomarkers of OS	Results
Leanza et al., 2023[15]	Postmenopausal women mean (SD) age 71.0 (5.7) years). N =31	12 with obesity	19 of normal weight	H_2O_2, MDA	H_2O_2, MDA increased with an increasing BMI, visceral fat mass, and trunk fat percentage
Uckan et al., (2022) 16	Females diagnosed with PCOD Total N= 139 ,	Study group 1- n=45 Obese with PCOD	Group 2 - Non-Obese With PCOD n=45Group 3: Healthy Control group n=49.	MDA SOD, GSH, GPx, CAT activities,	Significantly Higher MDA in obese females Lower levels of Antioxidants SOD, GSH and GPx higher CAT activity
Amin et al., 2020[17]	Female subjects N= 140	Study group n=70 – obese females	Control Group – n=70 non obese females	MDA vitamin C,	MDA significantly higher in obese group and low concentration of vitamin C in obese group
Jakubiak et al., 2021[18]	Both male and female subjects between 18 and 36 yrs	Group 1 n =16 Metabolically Healthy obese (MHO) Group 2: n= 61 metabolically unhealthy obese (MUO)	Control group n=345 metabolically healthy with normal weight (MHNW)	OSI, TAC, TOS MDA SOD	Antioxidant capacity (TAC) highest in MUO and lowest in MHNW. SOD activity significantly lower in metabolically unhealthy individuals

Jia et al., 2019[19]	N= 136 male Subjects sorted in 3 groups	Group 1: obese group BMI≥28kg/m2 n= 43 subjects) Group 2: overweight group (24<BMI<28kg/m 2 n=46 subjects)	Group 3 control group	MDA SOD Intraabdominal Fat (IAF)	Obese group had higher MDA, insulin resistance, and significantly lower SOD as compared to overweight group
Turner et al., 2021 [20]	older adults (mean age=66.2 y) At Risk of developing dementia N=65	overweight/obese (BMI ≥25 kg/m2).	healthy (BMI <25 kg/m2)	Glutathione	greater glutathione in the hippocampus compared with the healthy weight group
López-Domènech et al., 2018[21]	Obese subjects Divided in 3 groups. N= 225	Subjects with BMI, 30- 40 kg/m2 and >40 kg/m²	Subjects with BMI <30 kg/m2	total ROS, total superoxide, glutathione	Total ROS, total superoxide were selectively higher in the BMI > 40 kg/m² group.
Rowicka et al., 2017 22	Children with obesity divided based on their Z scores N=83	Group I (n = 62) Older than 5 years: BMI z-score 2SD; less than 5 years: BMI z-score 3SD.	In Control Group II (n = 21) who are not obese and have a BMI z-score of 1+1.	TOC , TAC TOC/TAC ratio, OSI	Obese children had significantly increased concentration of TOC and higher OSI, than nonobese.
Ranjit et al.,202123		100 Obese patients	100 healthy controls	SOD, GPx Vitamin C and Vitamin E	In obese patients (SOD), GPx,Vitamin C levels and Vitamin E levels were lower than normal range.

Abbreviations: Malondialdehyde (MDA) Superoxide dismutase (SOD), GPx Glutathione peroxidase, TOC Total Oxidant Capacity, Antioxidant capacity overall (TAC), oxidative stress index (OSI), catalase (CAT), body mass index (BMI), Metabolically Healthy obese (MHO) metabolically unhealthy obese (MUO), metabolically healthy with normal weight (MHNW

4.1 Characteristics of the Included Studies:

A total of 9 studies were included in the review that examined the association between Obesity and biomarkers of oxidative stress. Three of the studies included only female population (15)(16)(17) while only one was exclusively on male subjects (19) The Mean age of the samples were from 6.3 yrs – 71 yrs . Single study on Children (22) and two researches on geriatric group was included (15) (20). The sample size varied from 31 to 430 and the WHO BMI criterion for Obesity (WHO defines 18.5 kg/m^2 to 24.9 kg/m^2 as normal BMI, whereas a BMI ≥ 25 kg/m^2 falls in the overweight category and BMI ≥ 30 kg/m^2 is considered as obese) was considered in 7 of the studies. Study in Chinese population considered the guidelines for prevention and control of obesity commonly used in China. (19). The study on children considered z score (22) (BMI z-score, BMI for age 5-19 years overweight: >+1SD equivalent to BMI 25 Kg/m2 at 19 years , Obesity: >+2SD equivalent to BMI 30Kg/m2 (WHO) which is a normalized relative weight indicator independent of age and sex). Three studies of the nine explored the oxidative stress markers levels in subjects with existing disease condition PCOD (16) metabolically unhealthy obese (MUO) (18) and adults with risk of developing dementia (20).

Oxidative Stress Parameter: Five out of the nine studies measured plasma MDA levels a product of lipid peroxidation as an oxidative stress marker (15)(16)(17)(18)(19). SOD (Superoxide dismutase) was reported in five studies (16) (18) (19) (21) (23). Glutathione was assessed by magnetic resonance spectroscopy in the left hippocampus and the anterior and posterior cingulate cortex in only one of the studies (20) In Three other studies (16) (21) (23) plasma glutathione levels were assessed. For Antioxidant status TOC (Total Oxidative Capacity), TAC (Total Antioxidant Capacity), Oxidative stress Index (OSI), Vit C and Vit E levels were analysed in four of the nine studies.

5. DISCUSSION

This review reflects on the relation of oxidative stress with various grades of obesity and in different age groups. The main cause of obesity, which is a disorder of nutritional imbalance, is overnutrition. Obesity has proven to a major risk for several NCD’s which are implicated as compelling cause of mortality and morbidity in developed as well as developing nations.

Reactive oxygen species (ROS) are generated normally in the body as by-products of the process of electron transfer in the electron transport chain. (24) The Antioxidant system both enzymatic comprising of Superoxide Dismutase (SOD), GPx Glutathione peroxidase (GPx) and non-enzymatic- Vit C and Vit E serves to counters the pro oxidant environment created by ROS. An imbalance of the two with ROS prevailing over the antioxidant system causes oxidative stress. Oxidative stress (OS) has profound relevance in linking nutritional sciences to cell biology. Oxidative stress may be a contributor to the development of obesity related disorders and also a trigger to cause obesity. Elevated consumption of fats, carbohydrates, and saturated fatty acids—particularly trans-fatty acids—increases oxidative stress through a number of biochemical mechanisms, including the production of superoxide anion through oxidative phosphorylation, auto-oxidation of glyceraldehyde, activation of protein kinase C (PKC), and pathways involving polyol and hexosamine. (25)

Additionally, oxidative stress contributes significantly to the development of obesity by promoting the accumulation of adipose tissue and adipocyte growth, differentiation, and proliferation. (26) Present literature signifies the presence of oxidative stress in obese subjects but the heterogeneity of the biomarkers of oxidative stress and the homogeneity of the population and criterion for obesity studied induces the need for further exploring the issue. This review aims to summarize the studies of association of oxidative stress with obesity in different cohorts.

All of the nine selected studies showed increase in levels of oxidative stress parameters in obesity irrespective of the age of subject and status of existing disease condition. (Rowicka et al.,) showed the decrease in TAC and increase in TOC in obese children as compared to non- obese. These findings are similar to findings of (Killic et al.,) in which the TOC was found to be higher in the obese group as compared to non-obese but differed in their results of TAS. (27) TAS was found to be higher in obese children. A study in young adults revealed results that were in agreement to the results of (Killic et al.,) with TAC being highest in the metabolically unhealthy obese (MUO) group as compared to MHNW (Metabolically Healthy Normal Weight) (18).

This may be attributed to the counter resultant rise in TAS due to increased production of the Reactive oxygen species in obese group. Case control studies conducted on obese female population both postmenopausal (Leanza et al.,) premenopausal (Amin et al.,) and premenopausal with existing PCOD condition (Uckan et al.,) measured MDA as a marker for oxidation levels and SOD ,GPx (Uckan et al.,) and Vit c (Amin et al.,) as markers for estimating the antioxidant status.

Leanza et al., did not measure the antioxidant status in postmenopausal females. All three studies showed higher MDA levels in obese females and two of the three (16) (17) displayed lower antioxidant levels in the same group. Increase in the MDA levels was shown to have positive correlation with increasing BMI and the VAT (Visceral Adipose Tissue) and Trunk Fat by Leanza et al., (15).

These findings cognate with the findings of increased oxidative stress in obese females as compared to non- obese irrespective of their menopausal status. (28.). Turner et al., assessed the presence and levels of glutathione in left Hippocampus and the anterior and posterior cingulate cortex in older age obese who had a risk of developing dementia.

Difference in the levels of glutathione were seen in the hippocampus but no significant difference existed in anterior and posterior cingulate cortex between the obese and controls. The overweight/obese group had significantly greater glutathione in the hippocampus compared with the healthy weight group. (20) Also, the levels of glutathione did not correlate with the amount of activity (20). In an interventional study (López-Domènech et al.,) measured the oxidative stress parameters in leukocytes after a weight loss dietary therapy. The glutathione levels increased after the dietary restrictions in severe obese subjects. This resonates with the results of Bhatnagar et al.,that found the increases in Plasma glutathione levels after lifestyle modifications (29).

There are several possible contributors to oxidative stress in obesity, including hyperglycemia, (30) increased muscle activity to carry excessive weight. (31) Elevated tissue lipid levels (32) (33) inadequate antioxidant defenses (34) (35) chronic inflammation and endothelial ROS production, (36) (37) an increase in the amount of free fatty acids (FFA) in circulation is also a sign of obesity. Through protein kinase C (PKC), FFAs like palmitate increase the NADPH oxidase activity in smooth muscle and endothelial cells leading to increased production of ROS. (39)

In overweight and obese individuals, a lack of dietary consumption of protective antioxidant phytochemicals resulted in decreased plasma levels of vitamins and minerals, which increased oxidative stress. (40) (41). 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.

6. RESEARCH GAPS

Adipose tissue can be Visceral adipose tissue (VAT) or subcutaneous adipose tissue (SAT). SAT has a minimal contribution to or positive impact on cardiometabolic diseases, while expansion of VAT is recognised to be significantly associated with increased cardiometabolic risks (42). It is suggested that BMI cannot be the sole criterion to evaluate obesity , because the amount of VAT and ectopic fat significantly defines the risk of developing CVDs in overweight and moderate obese subjects (43). Visceral fat volume has been shown to be more associated with systemic endothelial dysfunction than subcutaneous fat (44) (45). Most of the above reviewed studies have taken BMI as the associative factor with oxidative Stress. Waist Hip Ratio, Intraabdominal fat ,Visceral Fat are known to have greater Relevance in oxidative stress and obesity related complications .

7. CONCLUSION DRAWN

Obesity is a proinflammatory condition and marked by increased oxidative stress, reduced antioxidants levels and increased levels of inflammatory markers both in diseased and healthy subjects of all ages. The levels of the markers tend to increase with age and degrees of obesity. Additionally, obesity is linked to several metabolic illness markers, suggesting that oxidative stress and inflammation may play a role in the relationship between obesity and metabolic disorders that are associated to obesity. More relevant criterion and indicators of obesity evaluation according to age, ethnicity and association to the disease need to be considered for further researches.

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