Original Article

Recapitulating The Etiology And Pathophysiology Of Obesity Epidemic: A Comprehensive Guide To Associated Biomarkers And Pharmacotherapy

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Abstract

Obesity or Adiposity is a worldwide common health problem that is related with an augmented risk of a number of medical conditions, morbidity and mortality. This mini review recapitulates the epidemiology, Etiology, associated comorbidities, biomarkers and available pharmacotherapy of obesity. The epidemiology of obesity is increasing in low-, middle- and high-income countries, with sociodemographic, behavioural, and genetic factors all playing a role. Comorbidities include hypertension, diabetes mellitus, stroke, coronary artery disease, and melanoma. Biomarkers associated with obesity include anthropometric markers, biochemical markers, hormonal markers, molecular biomarkers. Obesity related Oxidative stress is also discussed in this paper as per current findings from various clinical and preclinical data available up to January 2023.Treatment approaches range from lifestyle changes to pharmacotherapy and surgery. The available pharmacotherapy is either connected with precarious ill effects or overpriced, therefore, alternative therapies for obesity attenuation are required. Article under discussion provides an insight into oxidative stress attenuation, gene therapy via biomarkers regulation for combating obesity. Prevention strategies should include multidimensional approaches tailored to each nation

Keywords: Obesity, Etiology, pathophysiology, oxidative stress, biomarkers, Pharmacotherapy

INTRODUCTION

The global obesity pandemic has reached alarming proportions. According to the World Health Organization, obesity is defined as having a body mass index (BMI) of 30 or above. BMI is calculated by dividing an individual's weight in kilograms by their height in meters squared as given in fig1. A report from the WHO in May 2022 reveals that 60% of Europeans are overweight or obese[1]. This report also highlights the impact of the obesity pandemic, especially when compounded by the effects of COVID-19, on morbidity and mortality. The data shows that the prevalence of obesity is greater in women than in men of any age and increases with age, peaking between the ages of 50 and 65 years before slightly declining thereafter[2]. The age-standardized prevalence of obesity increased from 4.6% in 1980 to 14.0% in 2019. Similarly, the prevalence of obesity among children and adolescents has also risen significantly. The top ten ranked countries for obesity prevalence up to January 2023 are shown graphically in fig.2.[3]

The highest obesity rates can be found in the American and European regions, with the United States and Russia having the highest rates. With the serious health consequences of obesity, including comorbidities and mortality, concerted efforts from governments, the scientific community, individuals, and the food industry are required to address and control the obesity pandemic[4]

CATEGORY	BMI (Kg/m²)	OBESITY CLASS
UNDERWEIGHT	<18.5	
NORMAL	18.5-24.9	
OVERWEIGHT	25.0-29.9	
OBESITY	30.0-34.9	I
	35.0-39.9	II
EXTREME OBESITY	≥ 40.0	III

Figure 1: Obesity Classification (BMI-Body Mass Index)

ETIOLOGY OF OBESITY

Genetics, dietary habits, physical activity levels, socio-economic status and environmental factors all play a role in the development of obesity. Diet is a major factor in the prevalence of obesity. Eating a diet high in calories, sugar, and saturated fat can lead to weight gain and increase the risk of obesity, while consuming a diet rich in nutrient-dense whole foods such as fruits, vegetables, and whole grains, and low in processed and unhealthy options can help reduce the risk of obesity and promote overall health[5]. Additionally, portion size and the frequency of meals can have an effect on weight management. Eating larger portions or more frequently can contribute to weight gain, while being mindful of portion sizes and eating regular, balanced meals can help maintain a healthy weight[6]. It is crucial to adopt a nutritious, balanced, and sustainable diet in order to support a healthy weight and prevent obesity A sedentary lifestyle is characterized by a lack of physical activity and a tendency to engage in behaviours that involve little to no movement[7]. This type of lifestyle is often accompanied by obesity, as it can lead to an energy disproportion in which energy ingestion surpasses energy spent. An inactive lifestyle, combined with an unhealthy diet, can lead to the accumulation of excess energy in the body which is then stored as fat. This, in turn, can increase the risk of obesity. Engaging in regular physical activity and consuming a nutritious diet can help to prevent a sedentary lifestyle and the related risk of obesity[8].

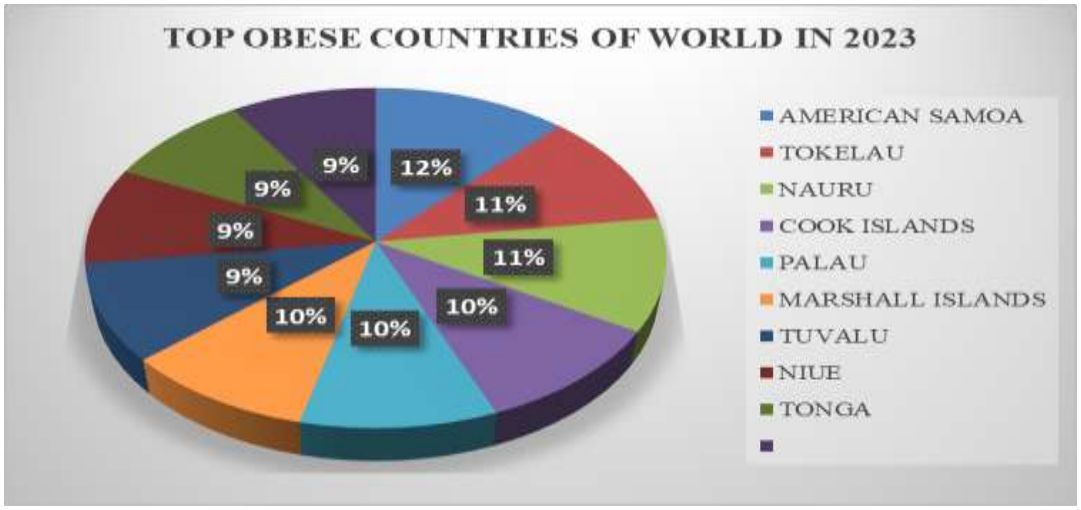


Figure 2: Obesity epidemiology January-2023

Socioeconomic factors can also contribute to the development of obesity. Studies have revealed that individuals with lower income and educational attainment are more likely to be obese when compared to those with higher income and educational levels. This may be due to a variety of aspects, such as the convenience and approachability of healthy food options, as well as time and financial constraints that can make it difficult for individuals to engage in regular physical activity[9]. In addition, certain cultural and societal norms may also contribute to unhealthy behaviours and an increased risk of obesity. It is important to address these socioeconomic factors in order to effectively address and prevent obesity in these populations. Genetics can impact the risk of obesity, as certain genetic variations may increase an individual's likelihood of developing obesity[10]. However, it is important to note that genetics is not the only factor involved, and the development of obesity is also influenced by environment and lifestyle. While genetics do play a role in the development of obesity, they are not the sole determining factor. While certain genetic variations may increase an individual's risk of obesity, they are typically only one part of the equation[11]. Environmental features, likewise diet and physical movement

levels, also play a significant role in the development of obesity[3, 12]. In fact, earlier studies have shown that the interaction between genetic and environmental factors is what ultimately determines an individual's weight and risk of obesity. While it is true that genetics can influence weight, they do not dictate it. It is important to remember that individual habits, such as meals and exercise, can have a powerful impact on people's weight along with overall health regardless of their genetic risk for obesity[13].

Pathophysiology of Obesity

Obesity is associated with an accumulation of excess fat and an increase in body weight and size in the skeletal muscles, liver, and subcutaneous and visceral adipose tissues. This excess weight is associated with higher resting energy expenditure, cardiac output, blood pressure, and insulin secretion, as well as an increase in macrophages and other immune cells in adipose tissue that secrete proinflammatory cytokines and lead to insulin resistance. Additionally, individuals who are obese may experience obstructive sleep apnea due to an excess of pharyngeal soft tissue, and an increased risk of osteoarthritis and gastrointestinal issues such as gastroesophageal reflux disease and oesophageal cancer. Obesity is also typically associated with an increase in plasma free fatty acids (FFAs) and an accumulation of excess lipids in white adipose tissue (WAT). The elevated levels of FFAs can inhibit the translocation of adenine nucleotides and promote the generation of oxygen in the mitochondrial electron transport chain while also stimulating the production of reactive intermediates through the activation of NOX by protein kinase C (PKC) in cultured vascular cells. Furthermore, conjugated fatty acids are prone to oxidation, which can trigger the formation of radicals and raise the presence of oxidative by-products. In obese individuals, higher concentrations of 4-hydroxynonenal (4-HNE) per unit of intramuscular triglycerides have been observed, indicating a greater susceptibility to oxidative modification. Additionally, the greater amount of lipid molecules in obese people may make them more vulnerable to oxidative modification by reactive oxygen species (ROS). Animal studies have also linked obesity to an increase in lipid peroxidation in WAT and a decrease in the expression and activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in WAT. Moreover, the intake of specific lipids, such as conjugated linolenic acid, can increase systemic oxidative stress. Leptin, a hormone that is correlated with the amount of adipose tissue and elevated in obesity, can activate NOX and trigger the formation of reactive intermediates, as well as stimulate the proliferation of monocytes and macrophages, leading to the release of proinflammatory cytokines. To counteract the deleterious effects of obesity, it is important to consume a diet that is rich in antioxidants and vital minerals. The relation of lepin, ghrelin, adiponectin and insulin in obesity development is diagrammatically illustrated in fig.3.

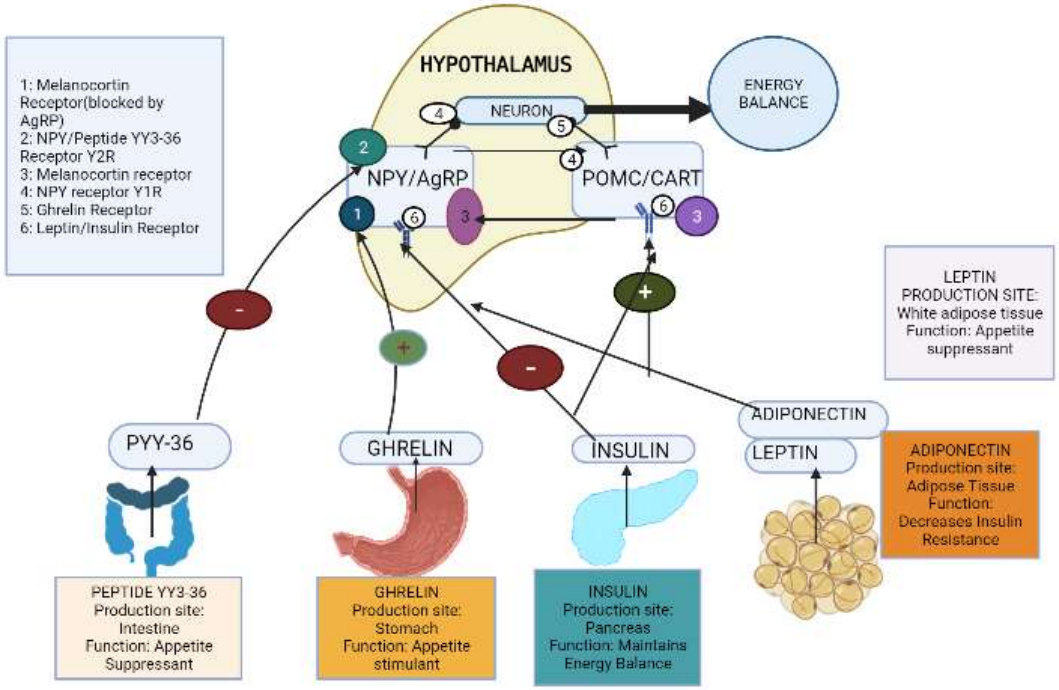


Figure 3: Role of ghrelin, leptin, adiponectin and Insulin in Pathophysiology of Obesity

Oxidative Stress and Obesity

Obesity has always remained related to an amplified risk of various health problems, many of which may be caused or exacerbated by oxidative stress[14]. Features that are often associated to cause oxidative stress in obesity include high blood sugar levels, high levels of fat tissue, nutrient deficiencies, chronic inflammation, and high levels of the hormone leptin, increased muscle activity due to carrying excess weight, impaired blood vessel function, impaired function of the energy-producing structures within cells (mitochondria), and dietary factors[15]. Biomarkers of oxidative stress, such as malondialdehyde, F2-isoprostanes, and protein carbonylation, have been found to be elevated in obese individuals[16].

Oxidative stress caused by obesity is associated with precarious ailments viz- insulin resistance, diabetes, heart problems, sleep disorders, asthma, cancer, reproductive problems, joint pain, and liver failure.[17]

Hyperglcemia, oxidative stress in obesity

Adiposity is meticulously related to insulin resistance and high blood sugar levels. When cells have too much glucose, it can lead to an overproduction of NADH and FADH2, which can cause an excess of protons to build up across the inner membrane of mitochondria. An excess proton gradient can cause electrons to leak out at complex III, leading to the production of superoxide, a type of free radical[18]. Superoxide can inhibit the enzyme glyceraldehyde-3-phosphate dehydrogenase, resulting in four different metabolic pathways that can contribute to oxidative stress: (1) the polyol pathway, which can cause a depletion of NADPH and an increase in the conversion of glucose to sorbitol, activating stress genes; (2) the hexosamine pathway, which can inhibit thioredoxin activity and cause oxidative and endoplasmic reticulum stress; (3) the formation of advanced glycation end products (AGEs) through the conversion of triose phosphates to methylglyoxal; and (4) the activation of the protein kinase C (PKC) pathway through the conversion of dihydroxyacetone phosphate to diacylglycerol [19]. These alternative pathways can lead to oxidative and nitro-stative stress through the production of free radicals or the impairment of antioxidant defences. Additionally, the auto-oxidation of glucose can produce reactive oxidants such as hydroxyl and superoxide radicals[20]. AGEs can bind to certain receptors on cells and promote the modification of signaling pathways and the production of additional ROS & RNS. The stimulation of the enzyme NOX and the transcription factor NF-kB can lead to an increase in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). This can result in the expression of proinflammatory cytokines, adhesion molecules, and microRNAs that are involved in inflammation and oxidative stress[21].

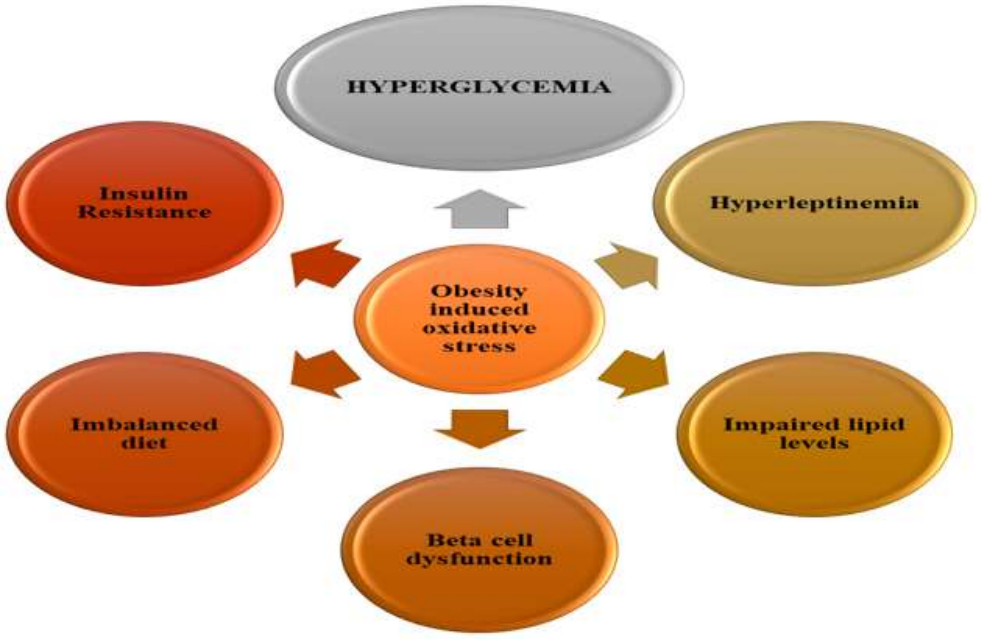


Figure 4: Pathogenesis of obesity induced oxidative stress

Lipid impaired levels linkage with oxidative stress and obesity

Overweightness is characterized by elevated levels of free fatty acids (FFAs) in the blood and excess fat storage in white adipose tissue (WAT). Elevated FFAs can stimulate the production of oxygen radicals in the mitochondria and promote the activation of the enzyme NOX through the protein kinase C pathway. Conjugated fatty acids, which are prone to oxidation, can also generate radicals and contribute to the accumulation of oxidative byproducts[22]. The higher concentration of lipid molecules in obese individuals may also make them more susceptible to oxidative damage by reactive oxygen species (ROS)[22]. Earlier reported data have revealed that excessive fat accumulation in WAT leads to increased lipid peroxidation and a reduction in the mRNA appearance and action of antioxidant in WAT. Consuming certain types of lipids, such as conjugated linoleic acid, has also been linked to increased oxidative stress in obese individuals [23].

Hyperleptinemia-oxidative stress and obesity

Leptin is a hormone released by fat cells, and its levels are directly correlated with body fat. In individuals with obesity, leptin concentrations in the blood tend to be significantly higher than normal. This increase in leptin has been linked to the development of oxidative stress, as leptin can activate the enzyme NOX, which stimulates the production of reactive oxygen species [24]. Studies involving animal models have shown that leptin injection can increase the levels of various biomarkers of oxidative stress, such as lipid hydroperoxides, malondialdehyde (MDA), isoprostanes, and protein carbonyls. Additionally, leptin has been observed to stimulate the production of proinflammatory cytokines and the

proliferation of immune cells such as monocytes and macrophages[17]. Leptin has also been associated with an increase in protein kinase C activity and macrophage lipoprotein lipase activity. In addition, leptin has been shown to inhibit the activity of the antioxidant enzyme paranoxase-1, leading to a rise in 8-isoPGF2a and higher concentrations of MDA and hydroperoxides in the blood [25].

Diet and Oxidative stress

Dietary choices can play a role in the generation of reactive oxygen species (ROS) in obesity. Eating a high-fat and high-carbohydrate diet can lead to an increase in oxidative stress and inflammation in obese individuals[26]. Additionally, a lack of protective phytochemicals with antioxidant properties, such as beta-carotene, vitamin E, and vitamin C, can leave individuals lacking an adequate antioxidant defence. Studies have found that dietary intake of antioxidant phytochemicals is associated with lower levels of obesity, body mass index (BMI), and lipid peroxidation [27]. It has also been observed that obese individuals have lower levels of trace minerals such as zinc and selenium in their blood compared to non-obese individuals, which are important cofactors for antioxidant enzymes. To reduce the risks associated with obesity, it is important to maintain a healthy diet that is rich in antioxidants, phytochemicals, and trace minerals [28].

Oxidative stress and b-cell dysfunction

Glucotoxicity and lipotoxicity are two major factors in the development of beta-cell dysfunction and type 2 diabetes. Beta cells have a low expression of antioxidant enzymes such as catalase and glutathione peroxidase, making them vulnerable to damage from ROS. Prolonged exposure to high levels of glucose and/or free fatty acids has been shown to increase ROS production and decrease insulin content and glucose-stimulated insulin secretion in beta cells [29]. ROS has also been shown to reduce insulin gene expression and insulin secretion through post-translational repression of transcriptional factors such as musculoaponeurotic fibrosarcoma protein A and pancreatic duodenal homeobox-1. The activation of uncoupling protein 2 (UCP2) by superoxide can also lower ATP levels and negatively regulate glucose-stimulated insulin secretion [30]. Mice with a deficiency in UCP2 do not experience the same decrease in glucose responsiveness seen in hyperglycemic and obese mice, indicating that this protein plays an important role in glucose homeostasis [31]. Additionally, the accumulation of lipids in adipose tissue, skeletal muscle, and other tissues can lead to an increase in free fatty acid concentrations, resulting in lipotoxicity and impairing insulin secretion [32].

Insulin Resistance and Oxidative stress

Obesity is allied to the expansion of several co-morbidities such as insulin resistance and diabetes, cardiovascular ailments, sleep illnesses, asthma, cancer, and liver failure. One of the mechanisms by which obesity may contribute to these conditions is through oxidative stress[33]. There are various factors that can lead to oxidative stress in obesity, such as hyperglycemia, increased lipid levels, vitamin and mineral deficiencies, chronic inflammation, increased activity of muscles to carry excess weight, impaired endothelial function, impaired mitochondrial function, and the type of diet. Hyperglycemia can cause the accumulation of advanced glycation end products (AGEs) in the body, which can cause oxidative damage to proteins and lipids [34]. Elevated levels of lipids can also lead to the accumulation of oxidized lipids, which can further contribute to oxidative stress [35]. There are several biomarkers that have been identified as indicators of oxidative stress in obesity, including malondialdehyde, F2-isoprostanes. Activities of antioxidant enzymes (SOD, GSH) are often observed to be lower in overweight individuals, and measures of radical quenching capacity such as ferric reducing antioxidant power and total antioxidant status are often lower in obese individuals as well [36]. Obesity-induced oxidative stress can lead to insulin resistance and diabetes through a variety of mechanisms, including the activation of stress-sensitive kinases, the modulation of transcriptional factors, and the management of glucose metabolism. Adequate intake of antioxidant phytochemicals and trace minerals may be protective against oxidative stress in obesity[37].

Inclusively, the association of oxidative stress & obesity is intricate and complex. More exploration is required to fully comprehend the mechanisms by which these 2 ailments are related and to develop efficacious approaches for preventing and treating obesity. There are several strategies that have been suggested for reducing oxidative stress in obese individuals, including weight loss, exercise, and the consumption of a healthy diet that is rich in antioxidants. Antioxidants are molecules that can neutralize ROS and protect against oxidative stress. Some dietary sources of antioxidants include fruits, vegetables, nuts, and whole grains

COMORBIDITIES IN OBESITY

Obesity can lead to a range of health issues known as comorbidities, which can portentously influence an individual's quality of life and lifespan[38]. Some common comorbidity linked to obesity include -1) Cardiovascular disease, including coronary artery disease, heart attack, and stroke, 2) Type 2 diabetes, a chronic condition marked by high blood sugar levels. 3) Musculoskeletal issues such as osteoarthritis and back and muscle pain 4) Sleep apnea, a disorder characterized by interrupted breathing during sleep. 5) Certain types of cancer, including breast, colon, and endometrial cancer[39, 40].

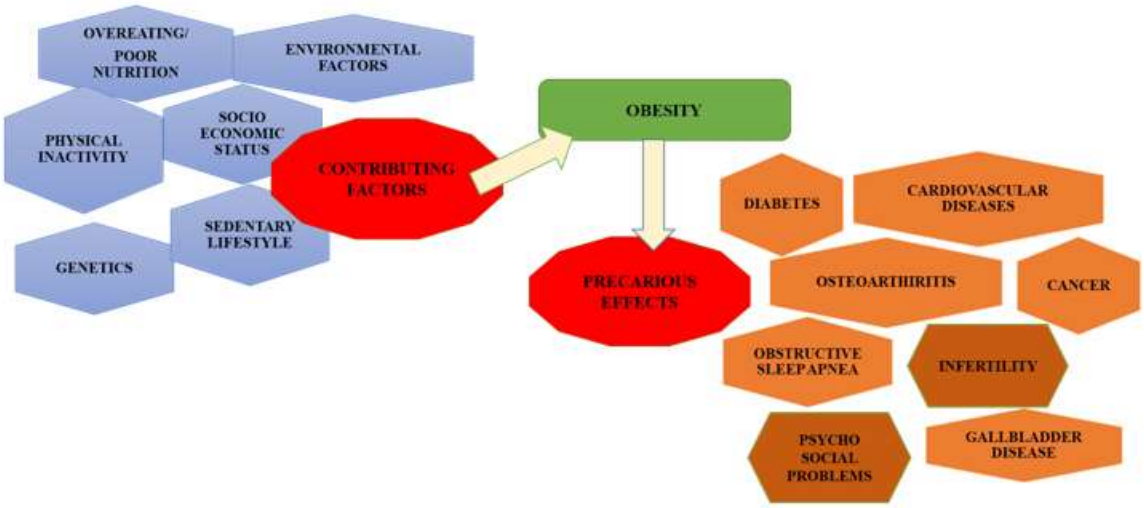


Figure 5: Etiology and associated ailments of obesity

Cardiovascular system ailments

Hypertension

Cardiovascular disease, a group of conditions affecting the heart and blood vessels, is a leading cause of death and disability worldwide. Obesity can contribute to the development of hypertension by several mechanisms, such as increased sympathetic activity, reduced parasympathetic activity, activation of the renin-aldosterone-angiotensin system (RAAS), and changes in kidney structure [41]. Certain ethnic groups, despite having higher rates of obesity, have relatively low rates of hypertension due to relatively decreased sympathetic activity[42]. The sympathetic nervous system can activate the RAAS system, resulting in fluid and salt retention, increased catecholamines, and further sympathetic activity. Adipocytes have also been found to produce angiotensinogen and angiotensin 2 independently [43]. Additionally, the kidney may have increased perinephric fat, causing compression and chronic inflammation, reducing blood flow and increasing sodium reabsorption, resulting in increased salt retention and further RAAS activation. This creates a self-perpetuating feedback loop, leading to further hypertension [44].

Heart Stroke

Research has shown that as Body Mass Index (BMI) increases, the risk of stroke correspondingly increases [45]. This was demonstrated in a national survey study which revealed that people with metabolically healthy obesity were still at a higher risk of stroke than non-obese groups, although the risk was lower than those with metabolically unhealthy obesity[46]. These results indicate that obesity is an independent factor in the development of stroke [47].

Coronary Artery disease

Coronary artery disease (CAD) is often associated with diabetes, hypertension, dyslipidemia, and obstructive sleep apnea, all of which are comorbid conditions of obesity [48]. While it is difficult to study if obesity alone can lead to the development of CAD due to the high prevalence of metabolic and respiratory comorbidities in the obese population, research has found that for every 5 unit increase in BMI, the risk of CAD increases by 30%.[49, 50]

Congestive Heart failure

Being obese is linked to a higher risk of congestive heart failure (CHF), even when taking other risk factors into consideration. Congestive Heart Failure (CHF) is believed to be caused by a multitude of factors[51]. These include an increase in left ventricular hypertrophy due to increased cardiac output, and reduced myocardial function due to lipotoxicity, inflammation and impaired protein function caused by increased glycosylation and collagen crosslinks, which leads to diastolic dysfunction [52]. In addition, the presence of increased epicardial fat and inflammation may exacerbate these effects[53].

Respiratory Problems

Obstructive Sleep apnea

During sleep, OSA is characterized by complete blockage of the airway despite normal breathing attempts. Obstructive Sleep Apnea (OSA) has a range of detrimental effects on the body, especially cardiovascular and metabolic effects thought to be caused by systemic inflammation [54]. These outcomes may include insulin resistance, dyslipidemia, hypertension, and coronary artery disease, for which OSA is also a standalone risk factor [55]. When the cardiometabolic consequences of OSA are combined with obesity, the risk of further negative outcomes is greatly increased [56].

Obesity Hypoventilation Syndrome (OHS)

In the absence of other causes, Obesity Hypoventilation Syndrome (OHS), also known as Pickwickian Syndrome, is characterized by three criteria: obesity, daytime hypercapnia, and sleep-disordered breathing [57]. The development of

OHS can be divided into two components: sleep-disordered breathing, which is a manifestation of OSA, and altered lung function and ventilatory control. During apneic periods, an excess of carbon dioxide accumulates and would normally trigger an increased ventilatory response to clear it [58, 59]. However, this does not occur in individuals with OHS. Instead, there is a gradual build-up of carbon dioxide, and the body adapts by increasing bicarbonate retention in the kidneys and reducing central sensitivity to carbon dioxide to increase ventilatory drive, leading to retention and ultimately resulting in daytime hypercapnia[60].

Diabetes Mellitus (type 2)

Obesity is prominent reason for the generation of type 2 diabetes mellitus. The exact mechanisms behind this alliance are still under investigation, but it is thought to involve both insulin resistance and beta-cell dysfunction. Insulin resistance happens when the body's cells become impervious to the action of insulin, leading to an increased demand for insulin production [61]. In obese individuals, excess fat tissue releases non-esterified fatty acids (NEFAs) into the bloodstream, which can cause inflammation and damage to the endothelial cells lining the blood vessels[62]. This can lead to insulin resistance and decreased insulin sensitivity in the body's cells. Beta-cell dysfunction refers to a decrease in the capability of the beta cells of the pancreas to generate and release insulin in response to increased blood sugar levels [63]. Obesity may contribute to beta-cell dysfunction through various mechanisms, including oxidative stress and inflammation. Overall, the combination of insulin resistance and beta-cell dysfunction caused by obesity leads to an impaired ability to regulate blood sugar levels and the development of T2DM.[64]

Dyslipidemia

Obesity is a foremost aiding factor in the development of dyslipidemia, a condition characterized by abnormal levels of lipids (such as cholesterol and triglycerides) in the blood [65]. Obese folks are at an amplified risk for dyslipidemia due to excess fat tissue, which leads to increased production of cholesterol and triglycerides. Additionally, obesity is associated with low levels of high-density lipoprotein (HDL) cholesterol that helps to remove excess saturated fat from the blood, and low levels of it can increase the menace of heart ailment and other cardiovascular complications[66]. Obesity may cause inflammation, which can stimulate the production of chemokines, proteins involved in the immune retort that can stimulate the liver to produce more cholesterol and triglycerides[67]. The combination of excess fat, low levels of HDL cholesterol, and inflammation can contribute to the development of dyslipidemia in obese individuals.[68]

Osteoarthritis

Obesity is a deep-rooted menace aspect for the progress of osteoarthritis, a common deteriorating joint ailment categorized by the cessation of tendon, the tissue that supports the ends of bones in linkages[69]. The excess weight carried by obese individuals puts additional stress on the joints, particularly in the hips, knees, and lower back, which can lead to the breakdown of cartilage and cause bones to rub together, resulting in pain, swelling, and reduced mobility. In addition, obesity is linked to inflammation, which can further contribute to the development of osteoarthritis. Inflammation in the joints can stimulate the production of enzymes that break down cartilage and other joint tissues, leading to joint damage. Overall, the combination of excess weight and inflammation increases the risk of developing osteoarthritis in obese individuals.[70]

Non-alcoholic Fatty Liver Disease, Gall Stones and GERD

Non-alcoholic fatty liver disease (NAFLD) is widespread in the US and UK, with around 30% of the population affected. It is predicted to be the leading cause of liver transplants in the US by 2030[71, 72]. The causes of NAFLD are still not fully understood, but it is associated with the metabolic disorders that come with obesity. There is a direct correlation between increased BMI and the presence of gallstones [73]. Even among individuals who are not obese, weight gain has been found to increase the risk of gallstones. Obesity has been linked to an increased risk of gastroesophageal reflux disease (GERD) due to factors such as non-specific motility disorders in the oesophagus, decreased lower oesophageal tone, higher rates of hiatal hernias, and elevated intra-abdominal pressures[74]. These conditions can lead to complications such as erosions, strictures, pre-cancerous transformations like Barrett's oesophagus, and even oesophageal adenocarcinoma as a result of acid reflux [75].

Infertility

Both men and women who are obese may experience fertility issues. In women, excess weight can disrupt the regular menstrual cycle and cause difficulties with ovulation[76]. Hormonal imbalances resulting from obesity can also lead to conditions like polycystic ovary syndrome (PCOS), which can impact fertility. Men who are obese may have lower testosterone levels and issues with sperm production, which can decrease their fertility[77]. Additionally, obesity can create physical barriers to fertility for both men and women, such as difficulties with sexual intercourse or problems with reproductive organs[78]. The association among obesity and fertility is intricate and complicated; therefore, it is essential for those trying to conceive are advised to maintain a healthy weight [79].

Cancer

Obesity has been related to an augmented risk of various types of tumour/cancer. It is assessed that almost 20% of all melanoma cases in the US are related to obesity. One way in which obesity increases cancer risk is through the production

of excess estrogen, which is a hormone that plays a significant part in the generation and growth of certain forms of melanoma, viz breast, uterine, and ovarian cancer [80]. Obesity can also cause higher estrogen levels in men owing to the translation of testosterone to estrogen in fatty tissues. Chronic inflammation, which is a recognized peril factor for cancer, could be caused by obesity. Inflammation can damage DNA and other genetic material which further initiates the expansion of lymphoma. Obesity is also associated with insulin resistance, which upsurges the menace of cancers, likeiwse pancreatic, colorectal, and breast cancer[81]. The physical effects of surplus body fat can also increase the risk of certain types of cancer. For example, abdominal fat can put pressure on the bladder and increase the risk of bladder cancer, excess liver fat could cause NAFLD and increase the risk of liver cancer, and excess fat in the neck and upper respiratory tract can put pressure on the esophagus and increase the risk of esophageal cancer [82]. Obesity can also increase inflammation in the body, which has been related to an amplified hazard of cancer. Inflammation is a normal retort of the immune system to wound or a contamination, but long-lasting inflammation could cause the development of cancer cells. The excess fat tissue in obese individuals can produce substances that contribute to inflammation, increasing the risk of cancer. Obesity is also connected with other risk factors for cancer, such as high plasma pressure, high blood sugar, and high cholesterol[83]. These conditions can all increase an individual's risk of cancer, particularly if they are not properly managed. Scientific data have shown that heavyweight people are more likely to develop these types of cancer, and their risk increases as their body mass index (BMI) increases[84]. To diminish the menace of melanoma, it is essential for individuals to maintain a healthy weight which can be accomplished through a combination of diet and workout, as well as other lifestyle changes such as quitting smoking and reducing alcohol consumption [85].

Psychosocial Problems

Obesity, a major concern that can influence folks of all ages and it can lead toward various physical and mental health issues. One aspect that is often overlooked in discussions about obesity is the potential for psychosocial problems, which are issues related to an individual's mental and social well-being that can be significantly impacted by obesity. Low self-esteem is a common psychosocial problem linked to obesity[86]. Obese individuals may feel self-conscious about their appearance and may feel that they do not fit in to societal standards of attractiveness, leading to feelings of inadequacy and a lack of confidence in social situations. It can also result in social isolation and discrimination[87]. Obese individuals may feel self-conscious about their appearance and may avoid social activities or situations where they may be judged or ridiculed, resulting in feelings of loneliness and a lack of social support that can harm an individual's mental health. Obesity can also impact an individual's employment and career prospects. Studies have shown that obese individuals may be less likely to be hired for certain jobs and may receive lower pay than their non-obese counterparts, leading to financial stress and a lack of fulfilment in one's career that can contribute to feelings of dissatisfaction and unhappiness[88]. In addition to these issues, obesity could leads to physical health problems such as diabetes, heart ailment, and joint problems. These physical health issues can further compound the psychosocial problems that an obese individual may experience. The physical limitations and discomfort caused by these conditions can make it harder for an individual to engage in social activities or work, leading to additional feelings of isolation and frustration. The stigma and negative attitudes often associated with obesity can also be a significant source of stress for individuals struggling with their weight. The constant criticism and judgment that many obese individuals face can damage their self-esteem and mental well-being. This negative social environment can also make it more difficult for an individual to seek help and support for weight loss, resulting in a cycle of continued obesity and related problems[89]. To address the psychosocial problems associated with obesity, it is important to address the underlying causes of the condition, such as unhealthy eating habits, lack of physical activity, and stress. It may also be necessary to address any underlying medical conditions contributing to an individual's weight gain. In addition to addressing these underlying causes, it is pivotal to make available the necessary support and resources for individuals struggling with obesity-related psychosocial problems[90]. This may include counselling and therapy to help individuals cope with low self-esteem and social isolation, as well as support groups and other resources to help individuals connect with others facing similar challenges[91].

Obesity Biomarkers

Obesity biomarkers are indicators that can be measured in the body to determine the presence or severity of obesity. These biomarkers can help classify those persons which might be at risk of obesity-related health problems or to track the effectiveness of interventions aimed at preventing or treating obesity[92]. Some commonly used obesity biomarkers include body mass index (BMI), waist circumference, and the presence of certain hormones or substances in the blood, such as leptin, insulin, and adiponectin. Other biomarkers that may be used include measures of inflammation, such as C-reactive protein or interleukin six & markers of metabolic function, such as blood glucose and cholesterol levels as depicted in fig.5. The specific biomarker chosen may depend on the goals of the assessment and the resources available for measuring the biomarker. Obesity biomarkers can be useful for identifying individuals who could benefit from obesity prevention or treatment and for monitoring the progress of such efforts[93].

Anthropometric markers of obesity

Obesity anthropometric parameters are physical measurements that can be employed to decide the existence or severity of obesity in a person. These parameters can help identify individuals who may be at risk for obesity-related health problems or to track the effectiveness of interventions aimed at preventing or treating obesity[94]. Some commonly used obesity anthropometric parameters comprise of body mass index (BMI), waist circumference, and waist-to-hip ratio. BMI

is a ratio of body fat founded in accordance with person's weight & height, and it is often used as a screening tool for obesity[95, 96].

The adiposity index is an evaluation parameter of body fat that utilizes a person's height, weight, and waist circumference to calculate their danger of obesity connected health problems, such as CVS disease, diabetes & certain tumour's[97]. It is obtained by dividing the waist circumference in centimetres by the height in meters and multiplying that value by 1.5. Higher values of the adiposity index correspond to a greater risk of obesity-related health issues. This index is a straightforward and easy-to-use measure of body fat that can be utilized in both population-based studies and clinical settings to assess the risk of obesity-related health problems. It is a useful alternative to other measures of body fat, such as body mass index (BMI), which might not always accurately reflect the distribution of fat in the body[98, 99].

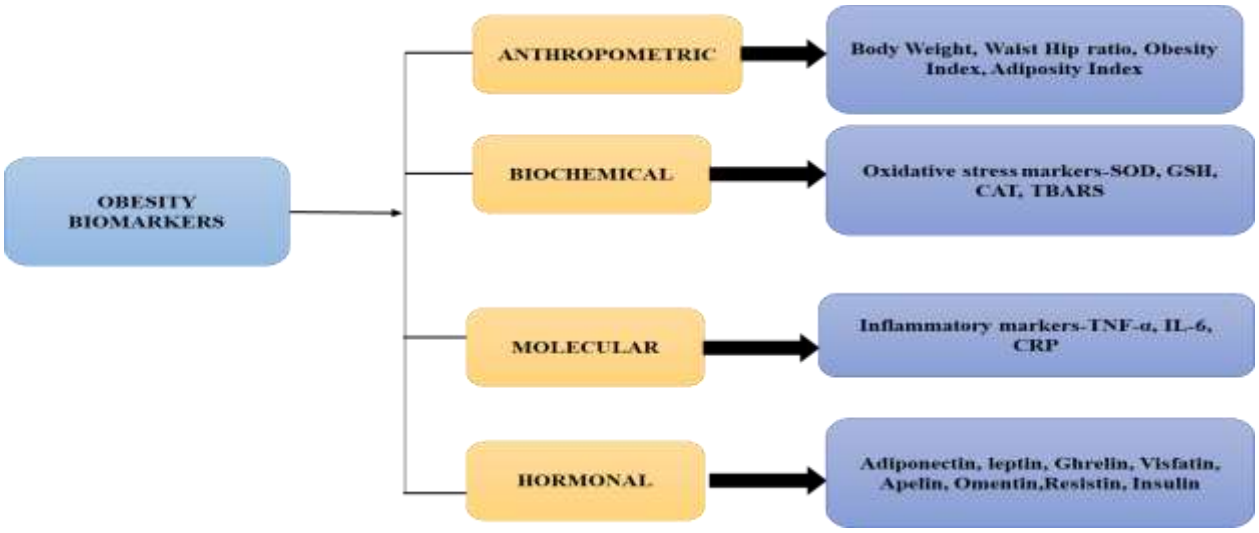


Figure 6: Biomarkers of Obesity (TNF-tumour necrosis factor, IL-Interleukin, CRP- C reactive protein,

The waist-to-hip ratio (WHR) is used to evaluate the arrangement or spread of body fat by dividing the waist circumference by the hip circumference. A high WHR, signifies a larger amount of abdominal fat compared to hip fat, is linked to a greater risk of these health complications[100]. The WHR can be used alongside other body fat measures, like obesity index and adiposity index, to assess the overall risk of obesity-allied health problems. To decrease the menace of obesity-allied health complications, it is important to maintain a healthy WHR in addition to a healthy obesity index and adiposity index[101].

Hormonal biomarkers/Circulating biomarkers of obesity

Adiponectin

Adiponectin is a hormone found in the blood that makes up about 0.01% of total plasma protein. It has been shown to have several positive effects on the body, including increasing insulin sensitivity, reducing inflammation, and protecting against heart disease. However, the exact way that it affects humans is not fully understood[102]. Adiponectin is found in three different forms in the blood: a trimer, a hexamer, and a high molecular mass form made up of 12-18 moieties. Some research suggests that the high molecular mass form may have stronger effects on insulin sensitivity and be more closely linked to it than the other forms. However, other studies have found that the low-molecular-weight form may be more important for reducing inflammation[103]. Despite being produced exclusively by fat cells, adiponectin levels are usually lower in people who are obese or have obesity-related conditions. Some experiments have recommended that it may have advantageous results on the heart and blood vessels, but others have not found such a link[104]. In addition, there is conflicting evidence on whether elevated levels of adiponectin are connected with a minor menace of heart disease or a higher risk of poor outcomes in high-risk individuals. Some research has also suggested that it might exhibit a part in lowering tumor risk, particularly for colorectal cancer, but this has not been confirmed in all studies. It is also unclear how adiponectin is related to HDL cholesterol and the relationship among intestinal obesity and colon cancer. Further exploration is required to fully comprehend the part of adiponectin in the body [105].

Leptin

Leptin is a protein that was discovered in 1994 and is primarily produced by fat cells. It exhibits a key role in controlling appetite, energy consumption & neuroendocrine function. People with mutations in the leptin gene often experience amplified food intake, raised insulin levels & chronic obesity[106]. Conversely, administration of leptin can reduce excessive eating and obesity in people who are deficient in it. However, in most people, leptin concentration upsurges with elevated body mass, indicating that they may become resistant to it [107]. This resistance may be caused by defects in the hypothalamus, which impair the capability of outlying leptin to initiate signalling in that region. People who have recently lost weight may have a relative deficiency in leptin, which can cause them to regain the weight[108]. This deficiency can be attributed to the fact that leptin circulates in the blood both as a free form and bound to a soluble

receptor[109]. The soluble receptor functions to regulate the level of bioavailability of leptin. Unfortunately, leptin therapy has not been successful in reducing body weight in common forms of obesity, but it has shown promise in people with rare mutations in the leptin gene[110]. New approaches are being developed to restore or increase sensitivity to the impaired function of the leptin receptor. Leptin has been linked to cardiovascular disease in some studies, but other research has not supported this association. Some studies have also proposed a probable role for leptin and the soluble leptin receptor in obesity-related cancers, but more evidence is needed to confirm this[111].

Resistin

Resistin is a small protein that is produced in the body and has been shown to stimulate the production of inflammation by activating immune cells called monocytes. It can also interfere with the action of insulin, leading to resistance to it. In rodents, resistin is produced by fat cells and is allied with obesity and insulin resistance[112]. However, in individuals it is mainly produced in immune cells called macrophages and may be more closely related to the immune response than to blood sugar control. Some research has suggested that resistin may leads to insulin resistance in adiposity and related conditions that cause inflammation[113]. It has also been linked to the development of a condition called atherosclerosis, in which the arteries become narrowed or blocked. As per reported data, it has been observed that people with elevated levels of resistin are at enlarged risk for insulin resistance, diabetes, and cardiovascular disease[114]. Various studies involving over 2000 people found that high levels of resistin are significantly associated with severe cardiovascular disease. Higher levels of resistin have also been linked to an increased menace of demise from any cause, particularly in people having diabetes or heart disease[115]. A recent study found that people with genetically higher levels of resistin had a twofold higher risk of death from any cause[116].

Apelin

Apelin is a protein that binds to the APJ receptor. It is found in the CNS and various tissues of the body, including heart and blood vessel walls. It is also produced by fat cells and is considered an "adipokine," which is a protein produced by fat cells that has an effect on the body[117]. Earlier reported literature has indicated that less content of apelin may be linked to an augmented risk of high blood pressure, particularly in people of Caucasian ethnicity. In addition, people with heart disease tend to have lower levels of apelin than healthy individuals that propose, apelin may have a defensive effect contrary to cardiac ailments [118]. Apelin is believed to have various effects on the body, including acting as an endocrine adipokine and regulating immune responses[119]. Overall, apelin is viewed as a beneficial adipokine and may be a potential lead for the attenuation of metabolic disorders & cardiovascular ailments and some forms of cancer[120, 121].

Omentin

Omentin, also known as abdominal lectin, is a protein that was originally discovered for its role in distinctive protection in contradiction to bacteria. It is primarily generated by visceral fat, but is also found in slighter ratio in dermal fat and in the gut tissues[122]. It is found in high levels in human plasma and has been linked to obesity & insulin resistance. It has also exhibited to improve blood vessel function and modulate inflammation, potentially through the nuclear factor B signaling pathway[123]. However, some studies have suggested that higher omentin concentrations may be linked with an amplified menace of heart illness and colorectal cancer, although this association may only be present in nonobese individuals. The exact role of omentin in obesity and cardiovascular disease is still being studied [123, 124].

Ghrelin

Ghrelin is a hormone that stimulates appetite and regulates the digestive system. It is produced by cells in the stomach and intestines, as well as the pituitary gland and other organs[125]. Ghrelin activates specific receptors in the hypothalamus, which is the part of the brain that controls appetite. The enzyme ghrelin O-acyltransferase attaches an acyl side chain to a specific amino acid in ghrelin, activating it[126]. Ghrelin has many functions in the body, including regulation of the immune and cardiovascular systems, and the promotion of insulin-like growth factor. However, its main role is in the gastrointestinal system, where it affects gastric emptying and intestinal motility. The importance of ghrelin in obesity is not entirely known, but some studies have suggested that obese individuals may have lower levels of postprandial suppression of ghrelin, leading to an increased sense of hunger even after eating[127]. This may be due to dysfunction in the gene for ghrelin, production of antibodies that inhibit ghrelin's effects, or other factors. More exploration is required for improved relationship amid ghrelin & obesity[128].

Insulin

Obesity has long been known to be linked to impaired insulin-mediated glucose uptake, also known as insulin resistance. This can lead to hyperinsulinemia, which is characterized by high content of insulin in the systemic circulation[129]. It is believed that hyperinsulinemia may be a result of the pancreas secreting more insulin in an attempt to compensate for elevated blood glucose levels. However, more recent research suggests that the order of events may be reversed, with obesity first causing hyperinsulinemia and then leading to insulin resistance through downstream pathways[130]. Insulin resistance and hyperinsulinemia have been anticipated as probable links among obesity and long-term ailments- Cardiac illnesses & diabetes[131]. The insulin and insulin-like growth factor are closely connected and play a part in management of cell growth and division. High levels of insulin can increase the availability of active IGF-1, which has been allied to an amplified hazard of malignancy[132]. On the other hand, IGF-1 has been shown to improve glucose homeostasis and

reduce the burden of atherosclerotic plaque through its effects on oxidative and inflammatory processes and cell senescence. Biomarkers of the insulin and IGF axis have been studied in relation to chronic disease risk as a way to provide evidence for their role in disease development[63].

Visfatin

Visfatin is a protein molecule with a molecular mass of 52 kilodaltons and was 1st recognized in 2004 by Fukuhara et al as an adipokine with insulin-mimetic properties. Visfatin was named for its believed production from visceral fat tissue, although it has since been found to be produced in a variety of tissues, including subcutaneous fat, skeletal muscle, liver, immune cells, heart muscle, brain cells, and renal glomeruli[133, 134]. The insulin-like effects of visfatin were demonstrated through its ability to reduce plasma glucose levels in mice, potentially through increasing peripheral tissue glucose uptake and stimulating the insulin signaling pathway[135]. The potential use of visfatin as a diabetes treatment has been explored, but findings on its relationship to type 2 diabetes mellitus and insulin resistance have been inconsistent. It is structurally parallel to pre-B cell group enhancing factor (PBEF), a chemokine with immune system and anti-apoptotic effects[136]. It is also related in the creation of nicotinamide adenine dinucleotide (NAD). NAD is a coenzyme that imparts a significant role in energy production and the amalgamation of regulatory proteins likewise sirtuins, which have been linked to metabolic processes and inflammation[134]. The ways in which visfatin may alter glucose and lipid metabolism through its NAMPT enzyme-like activity are not fully understood and require further investigation[136].

Inflammatory markers of obesity

Inflammation is a vital part of the body's response to injury, infection, and other triggers, such as obesity. Inflammatory markers are a type of biomarker that is used to measure the inflammatory response of the body. Inflammatory markers can be used to diagnose and monitor a range of conditions and diseases, including obesity[137].

Obesity is a condition that is characterized by an excessive accumulation of fat in the body. It is a major risk factor for a range of health conditions, including type 2 diabetes, cardiovascular disease, and certain types of cancer[138]. It is also associated with a low-grade systemic inflammation, which is thought to be responsible for the increased risk of obesity-related illnesses. This systemic inflammation is associated with increased levels of certain inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6)[139].

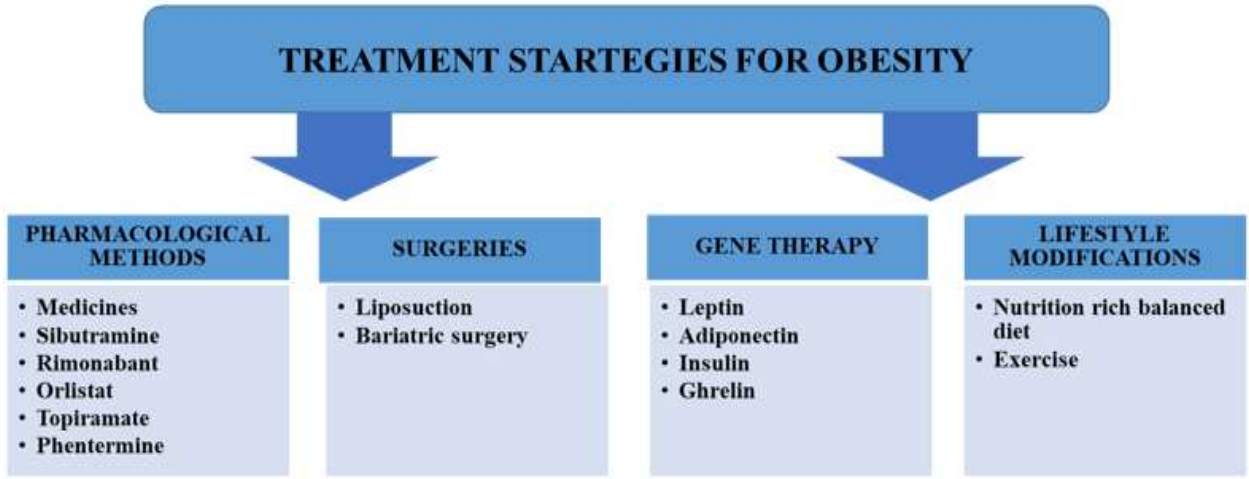
CRP is the main acute-phase protein produced by the liver and is used as a marker of inflammation. It is a sensitive marker that is often used to measure the level of inflammation in the body. It is also used to diagnose and monitor conditions such as obesity and cardiovascular disease. Elevated levels of CRP are associated with obesity and other medical conditions, such as diabetes, stroke, and coronary artery disease[140]. TNF-α is a cytokine that is produced in response to inflammation. It is involved in a range of inflammatory conditions and is thought to have a role in the development of obesity. Elevated levels of TNF-α are associated with obesity and its associated metabolic disorders, such as type 2 diabetes[141]. IL-6 is a cytokine that is involved in both the acute and chronic phases of inflammation. It is thought to play a role in the development of obesity, as well as its associated metabolic disorders. Elevated levels of IL-6 are associated with obesity, type 2 diabetes, and cardiovascular disease[142]. White blood cell (WBC) count is another marker of inflammation. WBCs are part of the body's immune system and help to fight off infection and other triggers. Elevated levels of WBCs are associated with obesity, as well as other medical conditions, such as diabetes and stroke. Platelet count is also used as an inflammatory marker. Platelets are cells that help to form blood clots and are involved in wound[143].

PHARMACOTHERAPY OF OBESITY

The available treatment to combat obesity are medications, liposuction, bariatric surgery and Gene therapy[144] which are not devoid of side effects and sometimes causes economic burden too on patients undergoing surgeries[145, 146]. Currently, official medications by the FDA for the dealing with obesity are listed in Table1. [147, 148]. Bariatric surgery is a surgical weight loss procedure that is performed on individuals having a high body mass index (BMI) who had struggled to reduce weight through non-surgical means. It involves altering the size of the stomach or the way the intestines absorb nutrients in order to facilitate weight loss. This type of surgery is typically reserved for severely obese individuals and at a high risk for obesity-linked health problems, such as hyperglycaemia, osteoarthritis, hypertension and cancer. It is a crucial technique that carries risks and requires a dedicated commitment to healthy habits in order to attain long-lasting achievement in weight reduction. Though, it is a successful method to permanently treat obesity, but it is not so economical method and it also have serious side effects such as malabsorption of nutrients due to gut hormone disturbances (nutritional deficiencies), hypoglycaemia [149-152].

Liposuction is a invasive practice that confiscates excess fat from person's body via a thin, hollow stainless-steel tube called a cannula which is implanted via minor cut in the skin and is used to suction out fat deposits.[153, 154]. This procedure is often used to target specific areas of the body with excess fat, such as the abdomen, thighs, buttocks, and arms. However, it is not a treatment for obesity and is typically only recommended for individuals who are already at or near their ideal weight, but have isolated pockets of fat that are resistant to diet and exercise. Liposuction is not a substitute for a healthy lifestyle and does not provide a long-term solution in weight reduction regime. It is imperative to be aware of fact that,

liposuction carries risks and complications, and it is important to carefully consider these before deciding to undergo the procedure. Liposuction is not in the reach of common man as it is highly expensive and poses precarious effects on patients [155-157].



Gene therapy is a potential treatment method for obesity, which is a significant contributor to various health problems such as cardiac disease, diabetes, and cardiac stroke. This method involves utilizing genes to prevent or treat a disease. In regards to obesity, gene therapy may involve introducing genes that increase the metabolism of fat cells or decrease the production of appetite-stimulating hormones (leptin, ghrelin and adiponectin). This approach has the potential to target the vital reason of obesity and may result in long-lasting weight reduction and better-quality life. However, gene therapy is still in the early stages of development, and more research is necessary to fully understand its safety and effectiveness. Indeed, it is a novel technique that can be employed for obesity management; nevertheless, its accessibility is not a cup of tea for all social-economic class of people [158-160] owing to its less accessibility and expenditure of therapy.

In the management of obesity, it is essential to make lifestyle modifications to improve general well-being and reduce the menace of interrelated health problems likewise cardiac disease, diabetes, and stroke. These modifications can include dietary changes, increased physical activity, and behaviour modification. To make dietary changes, one may need to reduce the intake of high-calorie, unhealthy foods and upsurge the eating of vegetables, fruits and whole-meal. Regular physical activity helps burn calories, improve cardiovascular health, and improve mood. Behaviour modification techniques may include setting achievable goals, seeking social support, and tracking food intake and physical activity. Although making these lifestyle changes can be difficult, they can provide significant long-term benefits for individuals with obesity.

Table 1: Us FDA Approved Drugs for Obesity Management

S.no	Drug/Approval Year (reference)	Mode of action	Clinical finding	Adverse Effects	Long term usage /short term usage
1.	Gelesis100/ 2019[161]	Superabsorbent aqueous-gel elements of a matrix composed of citric acid	Upsurges ampleness	abdominal distension, sporadic bowel motion	Long term use
2.	Liraglutide (3.0mg)/ 2014[162]	GLP-1 receptor protagonist	Reduced craving, elevates fullness, enhanced satiety	nausea, vomiting and abdominal pain	Long term use
3.	Bupropion or naltrexone (Contrave)/2014[163]	Amalgamation of dopamine and noradrenaline re-absorption blocker and antagonist of morphine like receptor	Reduces appetite and hunger	vomiting, constipation, pain in head, vertigo, sleeplessness, xerostomia	Long term use
4.	Phentermine-topiramate/ 2012[164]	Mixture of adrenergic components and carbonic dehydratases blockers	Reductions in appetite and rampage eating behaviours	vomiting, constipation, pain in head, vertigo, sleeplessness, xerostomia	Long term use
5.	Orlistat (Alli, Xenical)/ 1999[165]	Abdominal lipase prohibitor	Diminishes fat absorption by up to thirty percent	vomiting, constipation, pain in head, vertigo, sleeplessness, xerostomia	Long term use
6.	Diethylpropion/1979[166]	Sympathomimetic	Appetite suppression	hypertension and high pulse rate, less sleep, constipation, and xerostomia	Short term use
7.	Phentermine/1959[167]	Sympathomimetic	Appetite suppression	Headache, insomnia, palpitations, nervousness, increased BP	Short term use

Herbal remedies, which are derived from plants and believed to have medicinal properties, have gained popularity as an alternative approach for treating obesity. Some common herbs used for this purpose include green tea, ginger, and garcinia cambogia. Green tea is believed to have a thermogenic effect, which means it can increase the body's metabolism and

promote fat oxidation. Ginger has anti-inflammatory properties and may help to reduce appetite. Garcinia cambogia, a tropical fruit, contains hydroxycitric acid, which is thought to inhibit fat synthesis and reduce appetite. While herbal remedies may be effective in some cases, it is imperative to consult with a medical practitioner prior starting any new treatment, as some herbs may interact with medications or have potential side effects.

CONCLUSION:

In conclusion, obesity is a growing public health concern and it is essential to understand its etiology and pathophysiology as well as the available treatments. Pharmacotherapy and herbal approaches are both effective for treating obesity, as are dietary and lifestyle modifications. It is also important to understand the strategies for combating oxidative stress associated with obesity. With this information, it is possible to develop an effective treatment plan for obesity

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