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Obesity: Medical Consequences and Treatment Strategies

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Abstract: Obesity, a pathologic state characterised by excess fat reserves, is a serious health problem that increases the risk of numerous medical complications and mortality. The disease arises as a direct consequence of alterations in regulating energy balance in the body. The recent global rise in the prevalence of Obesity and unavailability of effective anti-obesity drugs has created an urgent need to understand and identify the important aspects related to the disease. In this review, we provide a perspective on the factors influencing Obesity, Obesity-associated disorders, pharmacological interventions and several other important concepts related to the disease.

Keywords: Obesity, Type 2 Diabetes, Adipose tissue, Pharmacotherapy, Inflammation Orlistat, Sibutramine

INTRODUCTION

Obesity is a condition characterised by excessive accumulation of triglycerides in the adipose tissue that leads to increasing fat mass that eventually affects health [1]. It is a chronic disease similar to hypertension and atherosclerosis. The cause of obesity is an imbalance between the energy consumption and energy expenditure by the body. The excess energy stored in fat cells leads to either the enlargement of fat cells (hypertrophy) or increase in the number of cells (hyperplasia). It is this hypertrophy or hyperplasia of fat cells that is the pathological lesion of obesity. The clinical problems associated with the obesity arise either due to the mass of the extra fat or because of the elevated secretion of free fatty acids and several peptides from the enlarged fat cells.

The outcome of these two mechanisms are the adverse effects such as diabetes mellitus, cardiovascular diseases, gall bladder diseases, osteoarthritis and some forms of cancer. At a broader level, obesity is associated with disability, mortality and substantial health costs whereas at an individual level, it leads to a multitude of clinical problems as well as considerable social stigma [2].

Definition of overweight and obesity

The degree of adiposity relates to the Body Mass Index, defined as the ratio of weight (in kilograms) by the square of height (in metres). The classification of overweight and obesity using BMI values predicts information about increasing body fatness [3]. The World Health Organisation has proposed the classification of overweight and obesity that applies to both the gender and all adult age groups (Table 1). The weight status between and within the population are easily comparable and the individuals or groups at the risk of morbidity and mortality are also identified. The identification of priorities for intervention at an individual or group level can be determined, and effectiveness of such interventions can be assessed. However, taken into consideration that there are differences in the body proportions, the BMI may not relate to the same degree of fatness among different populations [4]. BMI also does not take into account the wide variation in the nature of obesity among different individuals.

Table-1: Classification of overweight proposed by WHO [5]

BMI(kgm^{-2})	Classification	Description
<18.5	Underweight	Thin
18.5-24.9	_	Healthy, 'Normal'
25.0-29.9	Grade 1 overweight	Overweight
30.0-39.9	Grade 2 overweight	Obesity
≥40.0	Grade 3 overweight	Morbid obesity

Waist circumference

The central adiposity is a surrogate for the precise measures of visceral fat like computed tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen and is determined by the waist circumference. Waist circumference is used to assess the overweight and obesity and measured at the midpoint between the upper border of the pelvis and lower border of the ribs. For men, the waist circumference $\geq$94 cm and $\geq$ 102 cm represent the increased risk and substantially increased risk of metabolic complications respectively. However, for women, the waist circumference $\geq$ 88cm represents a higher risk of metabolic complications. The waist circumference estimates the upper body fat deposition but provides no clue about the intra-abdominal /visceral fat [6].

Skin fold thickness

The measurement of skin fold thickness at multiple sites with the help of callipers provides a more precise assessment. Equations are used to calculate and predict body fat percentage based on these measurements. However, the method requires the accurate callipers and is subjected to variation between observers. No information is available about the abdominal and intramuscular fat. It's hard to measure in individuals with a BMI higher than 35kg/m^2 [7].

Bio-impedance

The method is based on the principle that lean mass conducts electric current better than fat mass. The measurement of resistance to a weak impulse of current applied to the extremities determines the body fat by using an empirically derived equation. The method is easy, convenient, safe and relatively inexpensive. Though the devices are simple to use, they do not predict the biological outcomes more precisely as simple anthropometrical measurements do [8].

Computed tomography or magnetic resonance imaging

These imaging techniques are regarded as the most accurate methods for measuring tissue, organ, whole-body fat mass as well as lean muscle mass and bone mass. They are used in research settings. It is accurate and allows measurement of specific body fat compartments. However, the equipment is extremely expensive, and cannot accommodate individuals with a higher BMI > 35kg/m^2. Due to a large amount of ionizing radiations, the CT scans cannot be used for pregnant women or children [9, 10].

EPIDEMIOLOGY OF OVERWEIGHT AND OBESITY

Obesity is a disease in which excess body fat has accumulated to such an extent that adversely affects human health. The economic costs of obesity are high in developed countries and are about 2 to 7% of total heath care costs [11]. Obesity is a common condition in almost every continent. During 1983-1986, the data collected from the MONICA study provided most comprehensive information in Europe by knowing that more than half the adult population (35-65 years of age) were either overweight or obese. On an average about 15% of men and 22% of women were obese [12]. The surveys in England and Wales have confirmed an increase in the prevalence of disease from 6% men and 8% women in 1980 to 17% of men and 20% of women in 1997 [13]. The data obtained from the National Health, and Nutrition Examination Surveys (88-94) has shown that about 20% of men and 25% of women in the US are obese [14].There is also increase in the prevalence of obesity in Latin America and the Caribbean. The increasing prevalence is confined not only to Europe and America, but a marked rise has been observed in all populations in Southeast Asia [15]. It's necessary to estimate the prevalence, costs and trends in obesity to assist the policy makers and public heath planners. It is necessary to compare the population-based BMI data of different countries so as to identify the risk and compare the burden of obesity in the various countries. A systematic analysis known as Global Burden of Disease Study 2013' used data collected by international bodies and organisations in different countries over three decades and it showed the global hazard of obesity across the world. In 2013, the US topped the list with 13 percent of the obese people worldwide, while India and China together accounted for 15 percent of the world's obese population, with 46 million and 30 million obese people, respectively. According to the study, the number of overweight and obese people globally increased from 857 million in 1980 to 2.1 billion in 2013, i.e. one-third of the world's population [16].

Costs

Obesity is highly expensive and requires significant expenditure (2-7%) of national health care budgets [11]. With increasing BMI, the use of medication and hospital cost increases. In a large health maintenance organisation, the average annual costs for individuals with BMI between 30-35 kg/m^2 were 25% higher compared to individuals with BMI of 20-25 kg/m^2 and 44% greater in those with a BMI greater than 33kg/m^2 [17]. According to data from National Centre for Health Statistics and Framingham Herd Study, the costs of lifetime treatment of individuals with BMI of 37.5 kg/m^2 of obesity-associated diseases was $10, 000 higher than for men and women with a BMI of 22.5 kg/m^2 [18].

Factors influencing Obesity

Obesity is a heterogeneous group of the condition and not a single disorder as the body weight is determined by an intricate interaction between genetic, environmental and individual behavioural factors. Though the genetic factors are of prime importance bu the large scale increase in the prevalence of obesity is

attributed to the environmental and behavioural changes raised from technological advances [19].

Genetic Factors

There is a considerable variation in the body weight and fat mass irrespective whether the environment is energy rich or energy lacking suggesting that the obesity is influenced by intricate interactions between environmental, genetic, developmental and behaviour influences. There is a substantial evidence for the heritability of obesity and compared with other complex diseases; the heritability estimates are high [20-22]. A lot of genes are identified in both rare and common forms of obesity with a significant role in its aetiology [23]. According to Thrifty hypothesis by Neel, it was proposed that the genes that make susceptible to obesity would have had a selective favor in populations that frequently faced starvation. The individuals who possess these genes in the present obesogenic environment might be those that overreact-not just by becoming overweight but extremely obese [24]. The identification and cloning of mouse "ob" gene and its human homologue leptin proved to be a landmark research for the field that eventually led to the identification of several genes involved in the appetite regulation. The other genes that account for the morbid human obesity include the leptin and its receptor, pro-opiomelanocortin, α-melanocortin stimulating hormone receptor and prohormone convertase-1. Apart from these genes, there are about 30 different Mendelian disorders that have overweight as significant clinical features [25]. The clinical forms of obesity are rare. Among them, Prader-Willi Syndrome is the most common. The transmission of the gene occurs as a chromosome/gene abnormality on chromosome 15. The syndrome is characterised by a floppy baby that faces difficulty in feeding. The children are of short stature, obese and mentally slow. Another syndrome is the Bardet-Biedl syndrome that occurs due to a defect in the chaperonin-like gene [26-28].

Environmental factors

The critical role of environmental factors comes from the westernisation of lifestyles in developing countries. A marked change in BMI has been frequently observed in migrant studies where population from a common genetic background live under different environmental circumstances. It was noted that the Pima Indians, inhabiting the United States are 25kg heavier than the Pima Indians occupying the Mexico. In Industrialised countries, the higher prevalence of overweight has seen in those with lower education and low income, whereas the reverse is seen in developing countries [29]. There is also a tendency for gaining weight after marriage and with increasing parity. The environmental factors influence obesity by acting through increasing energy intake and/or decreasing energy utilisation. Physical activity is the most fluctuating component of energy expenditure and accounts for about 20-50% of total energy usage. The weight gain is correlated with the low levels of physical activity. In a study carried out in individuals aged 20-74 by National Health and Nutrition Examination Surveys for ten years, it was reported that the individuals with low levels of activity gained more weight as compared to those with higher levels. In the USA, the risk of obesity is higher for children who watch television for 5 hours each day relative to those who watch less than 2 hours [30, 31]. In U.K, a study showed a close relationship between prevalence of obesity and proxy measures of physical activity like car ownership and television watching [32].

As far as the energy intake is concerned the individual macronutrients exert different consequences on eating behaviour or satiety. Fats have a low satiety capacity, and thus, individuals usually overeat when presented with high-fat foods [33]. The fat intake and consumption of fructose corn syrups in drinks have also contributed to the obesity epidemic [34-37]. However, a definite relationship between the food intake and prevalence of obesity remains unclear due to under-reporting.

Fetal nutrition

During the intrauterine development, the undernutrition of fetus may determine the later onset of hypertension, type 2 Diabetes, and of obesity, independent of genetic inheritance, thereby suggesting a possible long-term programming of gene expression as a result of altered intrauterine growth [38]. The intrauterine events have an impact on postnatal weight gain and lifetime fatness. The factors like maternal diabetes and maternal smoking influence the individual's risk for increased body weight and even diabetes in later life. The infants who are breastfed for more than three months may have reduced the risk of future obesity. Baker has hypothesised that the nutritional defects in uterus cause defects in the development of body organs leading to the programmed susceptibility that later interacts with environmental stresses to cause diseases many years later. The hypothesis was supported by the fact that there is an inverse relation between birth weight and systolic blood pressure in both men and women in later life. The highest average systolic blood pressure was observed in those with the lowest birth weight and highest current weight [39]. However, according to thrifty phenotype hypothesis, the predisposition of obesity and type 2 Diabetes is an adaptation to malnutrition by the developing fetus. Low birth weight may be due to a variety of intrauterine influences but predominantly caused by maternal malnutrition. It is proposed that the fetus adapts its metabolism and growth to the expectation of reduced availability of nutrition. These may have survival advantages *in utero* by targeting the nutrients to essential organs and in later life by increasing the ability to store energy as fat so as to provide energy when the food is scarce. But when there is an abundant supply of nutrition, these adaptations are

detrimental. The studies have shown that the low births have indicated that they are almost seven times more chances to have either impaired glucose tolerance or insulin sensitivity [40]. Moreover, the highest blood glucose levels were found in men who were lighter at one year of age but had most elevated BMI when aged 64. The hypothesis could work by some mechanisms like the deficiency of insulin production by pancreatic β-cells and changes in placental vasculature leading to poor maternal transfer of nutrients. The critical periods of pancreatic cell development are the fetal and early life. Apart from this, reports have also shown that the protein restriction by mothers during pregnancy can reduce the pancreatic vascularisation in the offspring. In Dutch, a study was carried out in which the study of cohorts that were born around the time of famine provide some of the most impressive evidence that the intrauterine fetal development is critical for the subsequent development of obesity. The prevalence of obesity was higher in those adults where fetal exposure to famine coincided with the first two trimesters of pregnancy compared to the control group that were not exposed to famine [41]. In contrast, the prevalence of obesity was lower in those who were exposed to famine in the third trimester or shortly after birth.

OBESITY AN IMBALANCE OF ENERGY HOMEOSTASIS

Obesity arises as a result of disruption in the energy homeostasis. Energy homeostasis is the critical balance between the energy intake and the energy expenditure by the body and is maintained by multiple mechanisms in all organisms. The basic biological units of energy are the molecules such as phosphocreatine, ATP and NAD^+. These energy-rich molecules are used for the maintenance of nearly all biological functions like intracellular signalling, protein synthesis, neuronal signalling and the maintenance of transmembrane gradients. We take food in the form of carbohydrates, proteins, etc. which are catalysed and finally absorbed by the digestive tract. Inside the cells nutrients are taken up and hydrolysed to generate ATP, CO_2, H_2O and heat. The regulations of energy intake which can be viewed as the outcome of satiety, appetite and pleasure sensations are dependent upon the central nervous system and represent the one side of the energy equation. The dysregulation of feeding behaviour contributes largely to high obesity rates due to the prevalence of inexpensive palatable foods that promote over feeding. On the other hand, there are several processes that contribute to energy expenditure including basal metabolic rate, diet-induced thermogenesis and physical activity. Basal metabolic rate is the energy utilised for cellular and physiologic processes like protein synthesis and biochemical processes like muscle tone, cardiovascular and brain function. Thermogenesis is another factor that contributes to energy expenditure but in adults, the thermogenesis represents a minor component of human energy expenditure. Physical activity is also one of the biological processes that contribute to energy expenditure. Except for adults, physical activity is responsible for less total energy expenditure of the order of 20-30% [42]. The reduced physical activity or sedentary lifestyles has played a part in the increasing prevalence of obesity.

Adipose tissue is the main depot of stored energy, and multiple mechanisms are evolved which maintain sufficient adipose tissue mass. The Central nervous system plays a vital role in the maintenance of energy balance and energy storage. The CNS relies exclusively on glucose and has evolved the mechanisms such that the carbohydrate levels are maintained. However, under conditions of starvation or, in particular, diet configuration, the liver uses Acetyl Co A to generate ketone bodies that can be used as an alternate fuel source by the brain. The peripheral organs send a stimulus to the CNS via three routes: hormonal, neural and metabolic. The hormones secreted by the peripheral organs including adipose tissue, pancreas and gastrointestinal tract constitute the hormonal factors and the carbohydrates, ketones, lipids, alcohols, amino acids, etc. constitute the metabolic factors. The signals from the peripheral organs to the CNS are transmitted by the autonomic nervous system. The CNS integrates these diverse signals, and the brain alters the sympathetic and parasympathetic tone so as to regulate the metabolism via autonomic neuronal pathways. The CNS also controls the satiety, appetite, feeding, behaviour and exercise. The brain monitors the short term energy intake and long-term energy reserves to modulate the energy intake and energy homeostasis and thus the brain is considered as a master regulator of energy homeostasis [43].

CLINICAL MANIFESTATIONS OF OBESITY

The consequences of energy imbalance in the body lead to severe effects on the regulation of carbohydrate, protein and fat metabolism. There is an increase in the levels of free fatty acids, triglycerides, blood glucose whereas a decrease in the levels of adiponectin, HDL. The increase in the fat reserves in the body lead to a rise in the concentration of circulating triglycerides which eventually leads to the decrease in the HDL cholesterol. The decline in the HDL level coupled with the increased work on the heart of providing blood to the peripheral organs may contribute to the progression of cardiovascular diseases. The increase in the levels of insulin is also one of the clinical manifestations of obesity.The increased insulin resistance and enhanced insulin demand can lead to defects in the pancreas and thus causing diabetes mellitus. The hypertriglyceridaemia leads to increased production of cholesterol in bile, and thus gallstone formation occurs. Due to altered energy metabolism, there is increased T3 production, and the sympathetic nervous system is also modified. Hypertension and endocrine changes are also associated with obesity [44].

RISK FACTORS ASSOCIATED WITH OBESITY

The increase in body fatness leads to marked changes in the physiologic function depending upon the regional distribution of the adipose tissue. The obesity results in the alterations in the cardiac function and changes in the total blood volume whereas the accumulation of fat around the thoracic cage alters respiratory function. The intra-abdominal and visceral deposition of fat contributes mainly to the development of elevated plasma insulin levels and insulin resistance, hypertension and diabetes mellitus and hyperlipidemia.

Obesity & Type 2 Diabetes mellitus

The overall fatness and the distribution of body fat effect glucose metabolism through independent mechanisms. The increasing upper body obesity is associated with a progressive increase in the glucose and insulin response. The posthepatic insulin delivery increases in upper body obesity leading to enhanced peripheral insulin concentrations that eventually result in peripheral insulin resistance (Fig 1).

According to different fat distribution, the fat reserves vary in their response towards hormones that regulate lipolysis. The lipolytic response to noradrenaline is more marked in abdominal than gluteal or femoral adipose tissue [45]. Cortisol also contributes to the enhanced lipolysis by inhibiting the antilipolytic effect of Insulin. These factors contribute to the elevated levels of free fatty acids from adipocytes into the portal system [46]. The increase in free fatty acids contributes to the increased hepatic gluconeogenesis and glucose release. The levels of plasma free fatty acids lead to an impairment of hepatic glucose production. The reduction in hepatic clearance of insulin leads to elevated peripheral insulin concentration and the downregulation of insulin receptors. Firstly, the pancreas responds by maintaining a state of compensatory hyperinsulinaemia with the decomposition of glucose tolerance being prevented. However, with increasing levels of free fatty acids, the insulin resistant individual can't continue with this state compensation, and thus, hyperglycaemia occurs. Insulin resistance and hyperinsulinaemia are both characteristic correlates of a dyslipoproteinemic state and lead to the alterations of plasma lipid content associated with obesity [47]. Reports have shown a close association between Type 2 Diabetes and overweight. In a study (Nurses Cohort Study), BMI was the primary predictor of the risk of Diabetes [48]. Compared with the normal woman weighing BMI< 21kg/m^2, the individuals having a BMI of 25 had fivefold increased risk of Diabetes, for BMI of 30kg/m^2 there was 28 fold increased risk whereas 93 fold increased risk for those women who have a BMI of 35kg/m^2 or greater. During the period of study, there was a 2.7 fold increased the risk of Diabetes for the women who gained 8-10.9kg/m^2 compared with the women of stable weight and similar results were also observed in men. The likelihood of diabetes was also associated with the distribution of fat tissue. The waist circumference of greater than 102cm elevates the risk of diabetes by 3.5fold [49, 50].

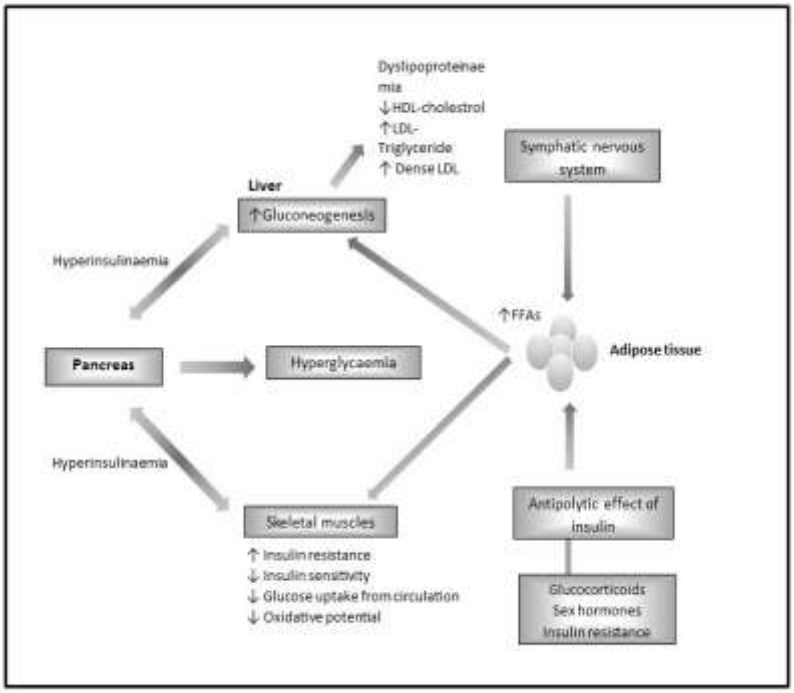

Fig-1: Schematic representation showing the association between obesity and Type 2 Diabetes

The detrimental effects of increasing amounts of fat tissue on whole-body sensitivity to the action of insulin in different organs are shown in the above figure.

Obesity & alterations in cardiovascular function

Overweight affects the cardiovascular function due to increasing total oxygen consumption as a result of expanded tissue mass as well as the increased oxidative demands of the adipose tissue which eventually leads to an elevation in cardiac output [Fig-2]. However, the values when normalised with body surface area are within the normal ranges [51]. Obesity leads to the increase in blood volume in proportion to body weight. The increase in blood volume leads to an elevation in left ventricular preload and an increase in resting cardiac output [52]. The increased demand for cardiac output is overcomed by an increase in stroke volume keeping heart rate unchanged. The increase in cardiac output and volume expansion lead to structural changes of heart whereas the increase in left ventricular filling leads to increase in left ventricular cavity dimension and increase on wall stresses [16]. The dilations in the left ventricle are consorted by myocardial hypertrophy. There is a direct relation between the increase in the left ventricular mass and the degree of overweight [53]. Since blood pressure is a direct function of systemic vascular resistance and cardiac output, thus elevated cardiac output in the obese patients leads to hypertension. The overweight and hypertension in combination leads to the thickening of the ventricular wall and increased heart volume and subsequently the greater chances of cardiac failure. In the Framingham heart study, it was reported that there was the direct development of congestive cardiac failure and increased body weight. Apart from congestive cardiac failure, there is a greater risk of morbidity from CHD, abnormal heart rhythms and even sudden death. In women with a BMI of 25 and 28.9, there was twofold increased risk of CHD and 3.6 fold for BMI>29, when compared with women with BMI<21 in the Nurses Cohort Study [54].

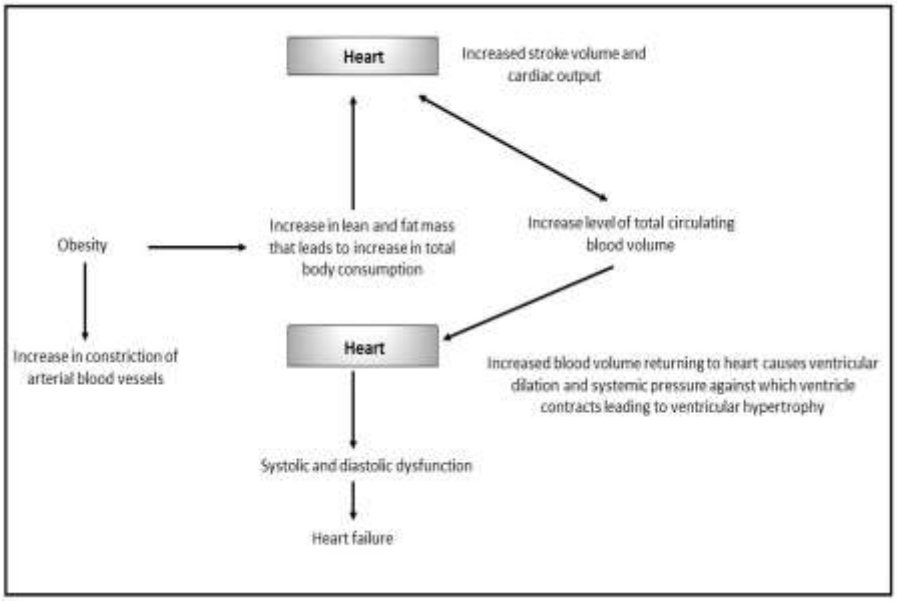

Fig-2: Schematic representation of alterations in cardiovascular functions in Obesity

The increased weight gain leads to physiologic changes in the cardiovascular function by affecting stroke volume, cardiac output and increased circulatory preload.

BREATHING ABNORMALITIES IN OBESITY

The alterations in respiratory events of inspiration and expiration arise due to the increased amount of fat in the abdomen and chest wall which affects the mechanical properties of the diaphragm. The increased fat mass demands an enhanced respiratory muscle force to combat the excessive elastic recoil. All of the obesity-related complications in respiratory functions affect mostly during sleep [55]. The studies carried out with overweight men and women have shown that obstruction in the larynx occurs and lead to loss of tone of muscles regulating tongue movements. The genioglossus muscle relaxes and allows the base of the tongue to fall back towards the posterior pharyngeal wall occluding the pharynx. This causes temporary alterations in breathing (apnoea). However, some of the obese patients develop a situation where a decrease in both hypoxic respiratory drives and carbon dioxide happens which are accompanied by an uneven pattern of breathing during sleep. The reports have shown that over 50% of men and one-third of women among 3034 subjects with BMI above 35 had snoring and apnoea complications [56]. Some groups have reported an elevated risk of myocardial infarction and stroke during sleep apnoea. The sleep apnea also increases the risk of cerebral infarction [57].

Obesity & Non-alcoholic fatty liver diseases

The obesity leads to alterations in the liver functioning like the steatosis, hepatomegaly, elevated liver enzymes, fibrosis and cirrhosis that are collectively referred as a Non-alcoholic fatty liver disease (NAFLD) [58]. The liver biopsy specimens of

obese and overweight individuals with abnormal liver biochemistries showed 10% prevalence of cirrhosis and 30% prevalence of septal fibrosis. The liver biopsies of obese patients also showed 75%, 20% and 2% prevalence of steatosis, steatohepatitis and cirrhosis respectively [59, 60].

Obesity & Gallbladder disease

The primary hepatobiliary pathology linked with overweight is cholelithiasis. In the Nurses' Health Study, it was reported that the incidence of clinically symptomatic gallstones was approximately equal to 250/100,000 person-year follow-up with the BMI<24kg/m^2 [61]. The rate increased gradually with higher BMI values. The possible explanation for the increased risk of gallstone formation is the increased cholesterol turnover associated to the total body fat. The cholesterol synthesis is directly related to body fat; 20mg of cholesterol are synthesised for each kg of extra fat. The high concentration of cholesterol excreted out in the bile, and the high level of cholesterol relative to bile acid increases the precipitation of cholesterol gallstones in the gallbladder [62].

Obesity & Cancer

Some forms of cancer are predominantly increased in obese patients. The cancers of the reproductive system are more frequent in women whereas in males there is increased risk for colon, rectum and prostate cancers. In overweight women, the higher risk for endometrial cancers arises due to increased secretion of estrogens by adipose tissue stromal cells. The increase in secretion is linked to the level of excess body fat that accounts for a major source of estrogen level in post menopause women. The increase in visceral fat assessed by computed tomography has also shown a significant relationship to the risk of breast cancer [63, 64].

Obesity & Endocrine changes

Several endocrine changes are linked with overweight. The most common affects the reproductive system as the rate of fertility reduces irregular menses and amenorrhea. The levels of hormones like adiponectin, ghrelin and growth hormone decrease whereas progesterone, cytokines (IL-6), Cortisol, leptin in plasma, androgens, TSH, etc. increases. Women with a BMI> 30kg/m^2 have irregularities in the secretion of pituitary LH, FSH and hypothalamic GnRH which lead to anovulation [65, 66].

Obesity & Psychosocial function

The obese individuals face the problems of public disapproval due to their fatness. The overweight women appear at higher risk compared to obese men due to enhanced societal pressures on women to be thin [66]. In a study (Medical Outcomes Study Short-Form Health Survey), the reports demonstrated that the overweight individuals presented for the treatment at the weight management centre had severe abnormalities in health-related quality of life and higher BMI values were linked with greater adverse effects [67]. However, it was seen that the patients who lost weight through gastric bypass showed improvements in all aspects of the study [68].

Diseases of joints, muscles, bones, connective tissue and skin

In overweight individuals, there is a significant increase in the risk for Osteoarthritis. The trauma associated with the level of excess of body weight leads to the development of osteoarthritis in knees [69]. The changes in the skin are also linked with excess weight like the stretch marks or striae. The expanding deposits of fat lead to increased pressure on skin folds that appear as stretch marks. The deepening of pigmentation in the folds of skin (knuckles, neck, knees, etc.) also appears in overweight individuals.

OBESITY; A CHRONIC LOW-GRADE INFLAMMATION

The increase in the morbidity and mortality risks associated with obesity elicited the interest in understanding the mechanism underlying the Pathophysiology of obesity. The discovery that the rise in the fat deposits in the body leads to an inflammatory state in metabolic tissues urged the research interests that address the inflammatory mechanisms in obesity. This inflammation associated with obesity termed as meta-inflammation is defined as chronic low-grade inflammation that arises in response to excess nutrients and energy [70]. The adipocytes act as connecting link between the metabolic input and inflammatory output [Fig 6]. The metabolic signals emerging from adipocytes initiate the inflammatory responses and disrupt the energy homeostasis. The first reports regarding the link between obesity and inflammation came from the studies where increased levels of cytokine TNF-α (Tumor necrosis factor-α) in obese mice compared with lean controls were observed [71]. After this study, some inflammatory cytokines like Interleukin-6 (IL-6) and IL-1β, CCL2 (Monocyte chemoattractant protein 1) and others were reported to increase in obesity [72]. In some cases, the moderate rise in the systemic levels of acute phase reactants in obese samples compared to lean control were reported. The hallmark of obesity-associated inflammation is that there is a moderate increase in the levels of cytokine expression compared with that of an infection, injury or acute immune response. The obese adipose tissues display significantly increased expression of protein kinases such as JNK, IKK and PKR. These kinases act as a major intracellular contributor of induction of inflammation in metabolic tissues. Also, the Toll-like Receptors of the innate immune system is also reported to get activated in obese patients compared to the lean subjects. In obesity-associated inflammation, the infiltration of immune cells into metabolic tissue increases. The study carried out in mice fed on a high-fat diet compared with mice fed on normal chow diet

showed that there was an increase in the macrophage population in the adipose tissue of obese mice. Apart from macrophages, the natural killer cells and mast cells are also reported to increase in obese adipose tissue and probably contribute to the metabolic Pathophysiology of obesity. The ratio of CD^{8+} to CD^{4+} T-cells also increases creating conditions favourable for immune activation. There are evidence that inflammatory responses are elicited by nutrients, e.g., the introduction of lipids into animal models resulted in inflammatory responses like JNK activation in liver and skeletal tissues. The inflammatory cytokine induction, macrophage infiltration, increased kinase activity was reported in the adipose tissue of obese humans compared with lean cohorts. Adipocytes not only serve as energy reserves but constitute the largest endocrine tissues that communicate with the other tissues by proteo-hormones, leptin, adiponectin and visfatin. Other gene products that contribute to adipocyte adipokines include the cytokines, complement proteins and growth factors. The inflammatory adipokines (TNF-α, IL-1, IL-6) are distributed by vascular system and lead to inflammation elsewhere. The visceral fat reserves secrete inflammatory adipokines that provide the pathophysiologic basis for comorbid conditions linked with obesity. The visceral adipokines are transported via the portal vascular system to the liver, elevating non-alcoholic steato-hepatitis and by systemic circulation to other areas. In addition to fatty acid lipotoxicity, the adipokine inflammatory response leads to pancreatic β- cell dysfunction that eventually decreases insulin synthesis and secretion. The TNF-α secretion increases relative to increased body fat mass and elevates inflammatory response in fatty liver, pancreas and gut visceral sites. The TNF-α, IL-6, C-reactive protein and specific amyloid contribute to inflammatory conditions such as NASH. The adipocytes stimulate fat associated macrophages that secrete MCP-1 (Monocyte Chemoattractant Protein 1), MMIF (Macrophage Migration Inhibition Factor) and resistin that enhance insulin resistance. These macrophages lead to the enhanced inflammatory state by activating MAPK finally, NF-κB and IRS-1 and 2 docking proteins. The docking proteins inhibit GLUT4 transporter of glucose thereby resulting in insulin resistance [73-75].

TREATMENT REGIMES FOR THE PREVENTION OF OBESITY

The lifestyle modifications, diet plans, adjunct pharmacotherapy and the surgical interventions are the mainstays for the management of obesity and obesity-associated disorders. The effective treatment strategies are designed based on the BMI values and the severity of the disease.

Lifestyle modifications

The diet, physical activity and behaviour therapy are the main components of the lifestyle changes. The low-calorie diets are designed based on the energy requirements that vary by gender, weight, the level of physical activity, etc. According to NHLB1/NAASO (National Heart, Lung, and Blood Institute/North American Association for the Study of Obesity) guide, the recommended low-calorie diets (LCDs) for overweight women are 1000-1200kcal/day and for overweight men about 1200-1600kcal/day (NIH Report, 2000). The patients who fail to lose weight by LCDs are given very-low-calorie diets (VLCDs). These diets are recommended for patients with BMI $\geq$ 30kg/m^2. VLCDs comprise 200-800kcal/day and sufficient amount of protein (70-100g/day) so as to preserve lean fat mass, but the diet should be used only under medical supervision.

Physical activity is one of the main contributors of lifestyle modification. The individuals who exercise regularly are more successful in maintaining weight loss. It increases calorie expenditure and facilitates the maintenance of weight loss in the presence of calorie restriction. The physical activity is of two types; programmed and lifestyle. The programmed activity includes walking, biking and aerobic classes, etc. The lifestyle activity includes the daily habits of using stairs rather than escalators, reducing the time for watching television and getting rid of sedentary lifestyles. The both types of activities along with diet produced a loss of approximately 8kg in 16 weeks. Behaviour therapy includes a set of principles and that helps the patients to facilitate their adherence to the diet and physical activity programmes. It includes self-monitoring of food and exercise, slow eating, stimulus control, cognitive restructuring and relapse prevention.

Pharmacotherapy

The drug treatment is recommended for individuals with a BMI $\geq$30kg/m^2 and for those who can't lose weight effectively with lifestyle modifications alone. The drugs that were approved by Food and Drug Administration (FDA) for the weight loss include the Sibutramine and Orlistat. Sibutramine is a β-phenethylamine that selectively inhibits the reuptake of noradrenaline, serotonin and acts by appetite suppression mechanism. The drug reduced weight loss dose-dependently in clinical trials with a weight reduction of up to 9% below baseline which can last up to 18 months with continued treatment [76]. When used in combination with diet therapy, the weight loss significantly reduced to 15% below baseline [77]. The drug is recommended for patients who are hypertensive or suffer from cardiovascular disorders, stroke, etc. The principle side effects of Sibutramine include insomnia, dry mouth and asthenia. The Orlistat (Xenical) is a lipase inhibitor that inhibits fat digestion. The Orlistat blocked the digestion of 30% of ingested triglyceride at a dose of approximately 120mg thrice a day. The drug produces weight loss of about 9-10% when used for one year [78, 79]. The gastrointestinal disorders like faecal urgency, oily spotting and increased defecation and the reduction in the absorption

of Vitamin E and β-carotene are associated with the use of Orlistat. Many anti-obesity drugs have been developed to date but due to several side effects associated with the drugs, they have been withdrawn. Some of the anti-obesity drugs and their current status are summarised in Table 2.

Table-2: Current status of Anti-obesity Monotherapies [80]

Drug	Mechanism of action	Side effects	Status
Dinitrophenol	Increase metabolic rate	Risk of neuropathy and cataract	**Withdrawn**
Amphetamines: Dexamphetamine, Methamphetamine	Appetite suppression	Cardiovascular adverse effects Dependency and abuse potential	**Withdrawn**
Amphetamine-like Analogues: Phentermine, diethylpropion, phenylpropanolamine	Appetite suppression	Increased risk of haemorrhagic Stroke	**Diethylpropion-available for short-term use (≤12 weeks) Phentermine-available for short-term use (≤12 weeks)**
Aminorex	Appetite suppression	Pulmonary hypertention	**Withdrawn**
Fenfluramine	Appetite suppression	Valvular heart disease, pulmonary hypertention	**Withdrawn**
Dexfenfluramine	Appetite suppression	Valvular heart disease, pulmonary hypertention	**Withdrawn**
Orlistat	Decreased fat absorption	Gastro-related disorders	**Available over-the-counter in several countries**
Sibutramine	Appetite suppression	Cardio vascular disorders	**Withdrawn**
Rimonabant	Cannabinoid receptor inhibitor	Potential of serious psychiatric disorders	**Withdrawn**

Surgical interventions

This is recommended for individuals with BMI $\geq$ 40kg/m^2 or BMI $\geq$ 35kg/m^{2}in the presence of comorbidities [81]. The surgical procedures are of two types; Vertical Banded Gastroplasty (VBG) and Gastric Bypass (GB). In both of them, a small pouch of the stomach (15-30-ml) with a line of staples is isolated which limits food intake. In the VBG, the pouch empties into the remaining stomach where the digestion continues normally. However, in GB not only the food intake is restricted but the reduction in absorption takes place by bypassing the remaining stomach and 45-150cm of the small intestine. The surgery reduces the average weight by 25% and 30% in VBG and GB respectively. The randomised trials have demonstrated that the patients who had undergone GB showed better maintenance of weight loss than in VBG. The screening procedure for bariatric surgery is rigorous. Pre-surgical consulting is done to ensure that obese patients should understand the post-operative dietary requirements. They should be aware of the risks of surgery like the operative mortality rate of approximately 1-5% [82, 83].

MEDICINAL STRATEGIES FOR THE TREATMENT OF OBESITY

The body weight is regulated by a feedback system where there are four main components:

a) Afferent signals like leptin that is secreted by the fat and it signals to the brain.
b) The Central Controller, which serves as a receiver for input signals and also an integrator of output signals. The Brain acts as the central controller.
c) Efferent signals that regulate food ingestion, food seeking and metabolism.
d) The controlled system that participates in digestion, absorption and energy storage [84].

Thus, the multiple sites in the body weight regulation system serve as targets for the treatment of obesity. The recent advancements in understanding the molecular mechanisms regulating the body weight are offering potential opportunities and renewed hope for the development of anti-obesity drugs. Based on available literature, several strategies have been designed that might lead to significant weight loss.

By reducing energy intake

This could be achieved either by amplifying food intake suppressing signals or by blocking food intake stimulating signals. The food intake is regulated both centrally as well as peripherally, and thus, some molecules involved in regulating food intake were targeted for drug development. The gastrointestinal peptides (cholecystokinin, gastrin releasing peptide, neuromedin B, etc.) reduce food intake both in animals and human beings. The peptide analogues have been designed although they have not reached the clinic. The pancreatic peptides like Glucagon-like peptide 1(GLP-1), enterostatin and amylin, modulate feeding behaviour

are also targeted. The molecules that regulate food intake centrally are the monoamines and neuropeptides, and most of them have been targeted for designing anti-obesity drugs. The noradrenergic target systems stimulate the noradrenaline (NE) release and block NE release whereas serotonergic target systems stimulate the 5-HT release and block 5-HT uptake. Leptin is one of the best candidates as it is the primary signal that informs brain regarding body fat. The identification of leptin through position cloning in 1994 proved a breakthrough in the history of obesity research. The leptin has been used in clinical trials where it showed promising results in leptin-deficient individuals. However it leads to significant discomfort at the injection site, and the limited effect was seen in clinical trials.

Targeting molecules involved in fat absorption

This strategy was used to design drug Orlistat, which was produced under the trade name Xenical. Xenical is a derivative of bacterial lipase inhibitor that inhibits pancreatic lipase activity thereby decreasing triglyceride digestion. Though the drug shows effective weight loss but has gastrointestinal side effects associated with it. Another strategy is to block the fatty acid uptake by the intestine. This requires the identification of intestinal fatty acid transporter like FATP4. These drugs, when designed, can have the potential advantage of preventing side effects that are associated with lipase inhibitors.

By Increasing Thermogenesis

This strategy involves the uncoupling of fuel metabolism and the generation of ATP such that the food energy is dissipated as heat. This approach has been used for more than 100 years and for this purpose thyroid extract was used. Based on this concept, dinitrophenol, a thermogenic drug was developed that produced significant weight loss but had undesirable side effects (cataracts and neuropathy). B_3adrenergic receptor agonists have the ability to increase energy expenditure and are currently being evaluated. The mitochondrial UCP-1(Uncoupling protein 1) has also been evaluated, but its use in humans is questioned owing to low levels of brown fat in humans.

By targeting fat metabolism

The enzymes involved in fat metabolism are also important anti-obesity targets. The proteins involved in adipocyte apoptosis, adipocyte differentiation, angiogenesis are important targets to reduce fat mass. One of the targets is the acyl-CoA diacylglycerol transferase (DGAT) which is involved in the triglyceride synthesis. This gene has been cloned, and the effects are being evaluated. The growth hormones like thyroid hormone, testosterones, etc. that regulate cellular metabolism are also of interest. However, the problem arises due to a reduction in visceral fat more than the total fat and cardiovascular diseases [85].

COMBINED DRUG TREATMENTS OF OBESITY

The previously designed anti-obesity monotherapies showed a reduction in body weight but were subjected to counter-regulation. This is evident due to the multiplicity and redundancy of mechanisms involved in appetite regulation and energy homeostasis. Therefore, the treatment strategies shifted towards the use of a combination of agents that target more than one biological mechanism and might lead to more efficient results. The first combination therapy for the treatment of obesity was designed by Weintraub *et al* [86]. The treatment included fenfluramine (a serotonergic drug) and phentermine (adrenergic drug). The combination of medicines produced significant weight loss and was able to maintain this weight off for more than three years during the study. The drug was widely used even before FDA approved it. Then after few years in 1997, the cases of valvular heart diseases were reported in patients using the combination of drugs and thus they were subsequently withdrawn [87]. Though this combination of medicines suffered severe drawbacks but the concept of designing new combinational drug therapies still continued and since then several combinatorial drug treatments were developed. Some of the drugs and their current status are mentioned in Table 3 [88].

Table-3: Current status of Anti-obesity Drugs (Polytherapies)

Drugs	Mechanism of action	Status
Tesofensine	5-HT/DA/NA reuptake blocker	Phase III
Dov 21947	-HT/DA/NA reuptake blocker	Phase II
Obinepitide	Neuropeptide Y2 + Y4 receptor agonist	Phase II
Contrave	Bupropion + naltrexone	Declined FDA 2011; cardiovascular concerns; company re-file probable
Empatic	Bupropion + zonisamide	Phase II
Qnexa	Phentermine + topiramate	FDA approved 2012, following re-file
Pramlintide/metreleptin	Amylinomimetic/leptin	Phase II; programmed terminated 2011; antibody generation

CONCLUSION

The rising epidemic of Obesity is quickly becoming a healthcare disaster in developed countries. The obesity associated health care systems is becoming unsustainable and immediate advances in treatment are required. The current pharmacological interventions in Obesity are limited by safety concerns and new policy directives aimed to combat disease are in need. The future of Obesity research is likely to mirror that of other chronic abnormalities; however, tackling a huge issue like Obesity requires multifaceted approach. The development of new drugs should also take into account the factors that impede the drug's efficacy like complex interplay of genetics, environmental factors, systemic pharmacotherapy and psychosocial issues. Understanding the progression of diseases, designing new treatment strategies coupled with knowledge and use of molecular techniques should accelerate progress towards gaining insight of Pathophysiology of the disease and ultimately the treatment.

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