Review Article

OBESITY : A COMPLETE REVIEW AND TREATMENT APPROACHES

Mujeeba Rehman [1] *, Syed Amir Zaid [2]

[1] Mahatma jyotiba phule Rohilkhand university, Bareilly Uttar Pradesh, INDIA.
[2] Birla institute of Technology and Science, Mesra, Ranchi, Jharkhand, INDIA.

ABSTRACT

Obesity is a condition in which excess body fat has accumulated that leads to negative effects on health. Weight higher than the consideration of healthy weight for a given height measured by screening tools like BMI (Body mass Index), waist circumference, waist to hip ratio and body fat percentage are defined as obese or overweight. Many pathological conditions are associated with obesity like hypertension, diabetes, mental conditions and even cancer. Since FDA approved only 4-5 drugs which are found safer to be used in this condition with few side effects therefore it is a need of an hour to conduct new researches for strengthening the treatment approaches for obesity so that this fire like rising threat to the society can be cured.

KEYWORDS: *Adipose tissue, Leptin, Orlistat, Orexigenic.*

1. INTRODUCTION

On global scale, obesity has reached epidemic proportions and is a major contributor to the global burden of chronic disease and disability. Currently, more than one billion adults worldwide are overweight and at least 300 million of them are clinically obese (WHO, 2009) [1]. Obesity and overweight recognised as chronic conditions which has emerged as one of the most serious global problem worldwide. The recent report of WHO (2012) estimated that worldwide 1.5 billion adults are overweight, among them over 200 million men and almost 300 million women are obese [2]. This word obesity had arisen from the Latin word *obesitas*, which means stout, fat, or plump. Medically, obesity is a condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and increased health problem [3]. Thus, the fundamental cause of obesity and overweight is an energy imbalance between calories consumed and those expended. The body needs a certain amount of energy, or calories, from food to sustain basic life functions. Body weight is maintained when calories eaten equals those used. When more calories as consumed then those burned, the overall energy balance is tilted toward weight gain, predisposing one towards being overweight and possibly obese [4]. Obesity could be iatrogenic i.e secondary to the drug treatments (antipychotics, antidepressents, antiepileptic, steroids and insulin) or due to certain diseases like Cushing

*Corresponding author:
Mujeeba Rehman
Mahatma Jyotiba Phule Rohilkhand University,
Bareilly Uttar Pradesh, INDIA.
* E-Mail: mujeebarehman94@gmail.com

syndrome, hypothyroidism etc). The identification of primary causes of this imbalance remains challenging and comprises the majority of cases usually diagnosed after causes for secondary obesity are ruled out. Various social and economic factors are responsible for causing obesity some of them including:-

➢ Lack of physical ability
➢ Chronic alcoholism
➢ Overconsumption of food and sedentary lifestyle

This chronic disease results from complex interactions of genetic, behavioural, and environmental factors correlating with economic and social status and lifestyles. Global strategies are focused on dietary and lifestyle modifications, i.e., restrict calorie intake and increase physical activity to slow obesity development. Researches demonstrated the potential of natural products to counteract obesity. Multiple natural product combinations may result in a synergistic activity that increases their bioavailability and action on multiple molecular targets, offering advantages over chemical treatments. The anti-obesity effects of these compounds are mediated by regulation of various pathways, including lipid absorption, energy intake and expenditure, increasing lipolysis, and decreasing lipogenesis, differentiation and proliferation of preadipocytes [5].

1.1 Introduction to obesity:

Obesity is a condition in which excess body fat (adipose tissue) has accumulated in relation to lean body mass to such an extent that health may be negatively affected. Overweight refers to increased body weight in relation to height, compared to some standard acceptable weight.

1.1.1 Methods to assess Obesity:
  a) Body mass index (BMI)
  b) Waist circumference
  c) Waist to hip ratio
  d) Body fat percentage

a) Body Mass Index (BMI): [5]
      BMI is simple and widely used method for estimation of body fat mass. It is true reflection of body fat percentage in majority of adult population. BMI is calculated by dividing the subject's weight by square of his or her height, typically expressed in metric or US customary units.

Metric: BMI = kg/ m^2

Where *kg* is the subject's weight in kilograms and *m* is the subject's height in meters.

US/Customary BMI = lb * 703 / in^2

Where lb is the subject's weight in pounds and in is the subject's height in inches.

Table No. 1.1: Classifiaction of obesity [5]

BMI	Classification
Less than 18.5	Underweight
18.5–24.9	normal weight
25.0–29.9	Overweight
30.0–34.9	class I obesity
35.0–39.9	class II obesity
Over 40.0	class III obesity

Some modifications to the WHO definitions have been made by particular bodies
- A BMI of 35.0 or higher *in the presence of at least one other significant comorbidity* is also classified by some bodies as *class III obesity*.
- For Asians, overweight is a BMI between23 and 29.9 kg/m² and obesity a BMI >30 kg/m².

The surgical literature breaks down "class III" obesity into further categories
- Any BMI > 40 is *severe obesity*
- A BMI of 40.0–49.9 is *morbid obesity*
- A BMI of >50 is *super obese*

      BMI of 25 will be considered clinically obese (compared to the earlier level of 30). A high BMI is predictive of death from cardiovascular diseases. Diabetes, cancer, high blood pressure and osteoarthritis are also common consequences of obesity and overweight.

b) Waist circumference:
      Waist circumference is a common measure used to assess abdominal fat content. The presence of excess fat in the abdomen, when out of the proportion of total body fat is considered an independent predictor of risk factors and ailments associated with obesity. Waist circumference is measured as the distance around the smallest area between the rib cage and above the umbilicus. The waist circumference considered as unhealthy for Indian men is now 90cm or 35.4" (it is 102cm/40.1" globally) and 80cm or 31.5" for Indian women (as opposed to 88cm/34.6").[6]

c) Waist to hip ratio:
      Waist to hip ratio is the ratio of person's waist size to hip size mathematically calculated as the waist size to hip size. For most people carrying extra fat around their middle have the health risks more than carrying weight around hips or thighs. The absolute waist to hip ratio (< 0.9 for men and < 0.85 for women) are both used as measures of central obesity. [6]

d) Body Fat Percentage:
      Body fat percentage is total body fat expressed as a percentage of total body weight. It is generally agreed that men with more than 25% body fat and women with more than 33% body. Body fat percentage can be estimated from a person's BMI by the following formula:

Body fat% = 1.2* BMI + 0.23* age - 5.4-0.8*gender
Where gender is 0 if female and 1 if male

2. Causes of obesity:
2.1 Genetics:
      There is a strong link between obesity and genetics. Proportion of causing obesity significantly increases if one parent is obese. A person can become obese or overweight for a lifetime if obesity develops at an early age. Studies conducted on effect of BMI to the genetic influences leads to the fact that major percentage of children can become obese if both the parents are obese whereas 20-30% chances are there if one parent is obese [7].

2.2 Diet:
      Individual's diet plays a vital role in being overweight or obese. Carbohydrate must be lower and protein diets somewhat higher may have some weight loss advantages in the short term.[8] Yet when it comes to preventing weight gain and chronic disease, carbohydrate quality is much more important than carbohydrate quantity. Diets that feature whole grains, vegetables, and fruits-seem to protect against weight gain, whereas western diets like highly fried food containing refined wheat flour more red meat or processed meat, sugared drinks and juices, sweets, refined carbohydrates, or potatoes-have been linked to obesity [9-10].

2.3 Exercise:
      Various socio-economic factors including lack of physical activity and sedentary lifestyles may increase the incidence of obesity. Higher levels of physical activity in obese patients are associated with a decreased risk of cardiovascular disease [11]. However, to what extent physical activity can counterbalance the risk associated with overweight and obesity remains unclear.

2.4 Pollution:
      In recent years, it has been known that various environmental factors besides these traditional factors can affect individual weight changes [12]. Chemical pollutants in environment such as benzopyrene have been shown to induce obesity. Some of the carcinogens which are known to cause effect on obesity like organochlorine pesticides and polychlorinated biphenyls cause targets adipose tissue [13].

2.5 Medications:
      Although various medications have been used to treat obesity and overweight persons but it can be iatrogenic that is many medicines can cause weight gain as side effect such as anti depressants drugs, hormonal medications, anti-diabetics, antipsychotics, corticosteroids etc.[14] therefore overuse of such

drugs should be avoided in case of obesity as it can worst the situation.

3. Importance of Study of Obesity:

Obesity has reached epidemic proportions in India in the 21st century, affecting a major percentage of the country's population. India is following a trend of other developing countries that are steadily becoming more obese. National family health survey (NFHS) in India conducted for various cities gives a data that represent the percentage of people rank wise in various states like Punjab, Kerala, and Goa the percentage of obese male and female is greater than 20 and in Punjab it is 37.5%.

Table No. 1.2: List of the states of India ranked in order of percentage of people who are overweight or obese, based on data from the 2007 NFHS (National family health survey, India) [15]

| States	Males (%)	Males (rank)	Female (%)	Female (rank)
PUNJAB	30.3	1	37.5	1
KERALA	24.3	2	34	2
GOA	20.8	3	27	3
ANDHRA PRADESH	17.6	5	22.7	10
SIKKIM	17.3	6	21	8
MIZORAM	16.9	7	20.3	17
GUJARAT	15.4	10	17.7	7

4. Pathophysiology:

Leptin and ghrelin are internal mediators that affect feeding and appetite. Ghrelin is produced by the stomach modulating short-term appetitive control (i.e., to eat when the stomach is empty and to stop when the stomach is stretched). Leptin is produced by white adipose tissue to signal fat storage reserves in the body and mediates long-term appetitive controls (i.e., to eat more when fat storage are low and less when fat storages are high). It plays a critical role in the regulation of body weight and energy balance by inhibiting food intake and stimulating energy expenditure.[16] Most obese individuals are thought to be leptin resistant and have been found to have high levels of leptin. This resistance is thought to explain in part why administration of leptin has not been shown to be effective in suppressing appetite in most obese people. They control appetite through their actions on the central nervous system. Thus, a deficiency in leptin signaling either via leptin deficiency or leptin resistance leads to overfeeding and may account for some genetic and acquired forms of obesity [17].

Fig. 1.1: Mechanism of obesity [18]

a. Hormonal regulators of hunger, satiety and adiposity are released from the periphery. These include leptin and other adipokines, and also inflammatory cytokines, from adipose tissue. Insulin and pancreatic polypeptide (PP) are secreted from the pancreas. Furthermore, ghrelin (also known as appetite-regulating hormone), pancreatic peptide YY (PYY), glucagon like peptide-1 (GLP-1, a cleavage product of glucagon) and cholecystokinin (CCK) are released from the GIT. These hormonal regulators of energy balance act on hindbrain & hypoythalamic brain sites to influence hunger and satiety.

b. Hormonal signals from the viscera that regulate energy balance & vagal nerve input that is related to stomach distension after meal ingestion, alter neuronal activity in the nucleus tractus solitarious (NTS). The NTS relays information related to energy balance to homeostatic feeding circuits in the hypothalamus.

c. In the arcuate nucleus in the medio basal hypothalamus, so called first order neurons that contain agouti related peptide (AgRP) & neuropeptideY (NPY) are activated by orexigenic signals and inhibit the so called second order neurons that express melanocortin 4 receptor (MC4R), and this tonically inhibits feeding behaviour. Conversely, anorexigenic signals activate first order neurons containing cocaine and amphetamine regulated transcript (CART) & propiomelanocortin (POMC), which stimulates the release of α-melanocyte stimulating hormone (α-MSH), a cleavage product of POMC. This results in the activationMC4R neurons and inhibition of feeding behaviour [18].

3.1. Pathologies associated with obesity and its effects on health:

Obesity is one of the leading preventable causes of death. Large scale American and European studies have found that mortality risk varies with BMI. A BMI of over 32 is associated with a doubling of risk of death and obesity is estimated to cause an excess 111,909 to 365,000 death per year in the United States. Obesity on average reduces life expectancy by 6-7 years. Severe obesity (BMI's> 40) reduces life expectancy by 20 years for men and 5 years for women. Health consequences can be categorized by the effect of increase fat mass (osteoarthritis, obstructive sleep apnoea) or by the increased number of fat cells (diabetes, cancer, and cardiovascular disease). Metabolic syndrome is a combination of medical disorders which often includes diabetes mellitus type 2, high blood pressure, high blood cholesterol and triglyceride levels. These can be tabulated as follows [19].
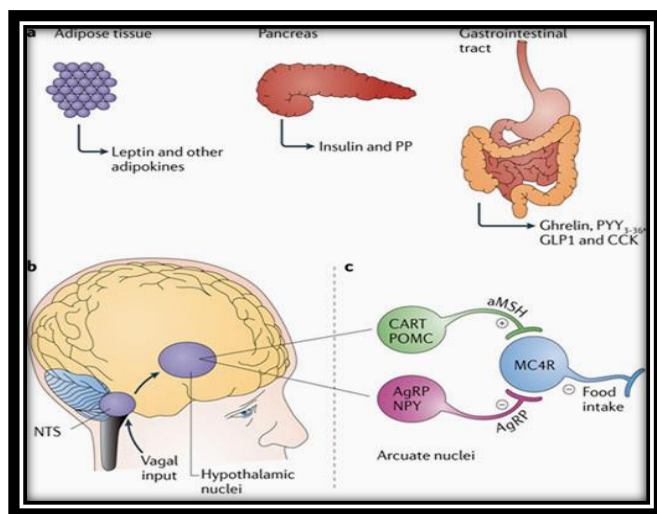
3.1.1 Obesity and hypertension:

According to the Centres of disease control and Prevention (CDC), approximately 30 percent of hypertension cases are due to obesity, and the figure may be as high as 60 percent in men under age 45. All the risk factors of heart disease, hypertension and stroke arises from high lipid level, especially LDL which is a bad cholesterol may accumulate as plaques leading to atherosclerosis and ultimately increasing the peripheral resistance thus leads to cause a high blood pressure. [20]

3.1.2 Obesity and diabetes:

In an obese individual, the amount of Non esterified fatty acids, glycerol, hormones, cytokines, pro-inflammatory substances, and other substances that leads to the development of insulin resistance are increased. Insulin resistance also increases with impairment of β-cell function due to lipotoxicity to the neighbouring non adipose tissues leading to the impairment of pancreatic cells dysfunction leads to the development of diabetes. Chances of diabetes type 1 increase if a person starts gaining weight at an early phase of life [21].

3.1.3 Obesity and cancer:

Several hypothesised mechanisms have been postulated for the association between diabetes and cancer, including the effects of hyperglycaemia or insulin resistance and hyperinsulinaemia and the latter promotes tumour cell growth directly via insulin receptors [22], but effects may also be mediated indirectly via the IGF-1 receptor and all this leads to many cancer cell lines express insulin and IGF-1 receptors [23]. Factors which promotes tumour includes increased cell growth, anti-apoptosis, increased cell motility and invasion.

Being overweight or obese increases the risk of 13 types of cancer:

Breast (in women after the menopause), bowel, womb, oesophageal (food pipe), pancreatic, kidney, liver, upper stomach (gastric cardia), gallbladder, ovarian, thyroid, myeloma (a type of blood cancer), and meningioma (a type of brain tumour) [24, 25].

3.1.4 Obesity and mood disorders:

Obesity may cause the prevalance of mental disorders in an individual. Approximately 25% of all adults in the United States have been reported to experience some mental health disorder each year.[26] Psychologists have found that obesity is considered as a "speck" on personality as it leads to social withdrawl. Obese people may be a target of teasing in public places and subject to discrimination or avoidance. Richardson et al.[27] conducted several experiments to rank preferences for 6 images of individuals (those with no physical handicap or some physical handicap and 10-year-old or 11-year-old obese children). They found consistent preferences for no handicap over some handicap. Remarkably, the least preferred image was always that of obese children [28]. This speck due to obesity may generate considerable stress, which can lead to mental health disorders.

4. Target sites of antiobesity drugs:
4.1 Pharmacological targeting of adipocytes/fat metabolism:

The discovery of the cytokine (now called and adipokine) leptin has motivated research that has revealed the adipocyte to be an endocrine cell at the centre of metabolic regulation which was generally considered to be a relatively inert tissue that merely responded to nutrient intake by storing fat. Leptin is made exclusively in adipocytes [29] and its deficiency (ob/ob mice) or a deficiency of its receptor (ob/ob mice) causes massive obesity and diabetes. There are three somewhat independent target classes in adipocytes that may be suitable for therapeutic intervention in obesity and diabetes:

a) Adipokines
b) Modulators of hormonal sensitivity, and
c) Enzymes involved in fat storage.

a) Adipokines:

Leptins: Leptin plays a major role in the regulation of food intake and metabolic rate [30], and the amount of leptin in circulation is proportional to the fat mass. However, most obese patients already have high levels of circulating leptin and are resistant to the actions of this adipokine even when exogenously administered.

Adiponectin: adiponectin has now become the generally accepted and most widely used name for this adipokine. Circulating adiponectin levels correlate with insulin sensitivity in humans; interestingly, injection of adiponectin in mice has been shown to enhance oxidation of fatty acids in muscle as well as decrease hepatic glucose production and induce weight loss.

b) Modulators of insulin sensitivity:

PPAR: PPAR are a family of three (α, δ, and γ) nuclear receptors that affect the transcription and expression level of numerous target genes in adipocytes and other tissues/cells. PPARγ plays a major role (probably the major role) in the differentiation of preadipocytes to adipocytes [31] the process of adipogenesis. Thus the drug regimen of PPARγ agonists rosiglitazone and pioglitazone results in enhanced differentiation of adipocytes, which unfortunately tends to cause weight gain in animals as well as humans. Peroxisome proliferator-activated receptor gamma (PPARγ) is ligand-activated transcription factor and functions as a heterodimer with a retinoid X receptor (RXR).

It is experimentally proved that moderate reduction of PPARγwith an RXR antagonist or a PPAR γ antagonist decrease triglyceride (TG) content in white adipose tissue, skeletal muscle and liver. These inhibitors potentiate leptin's effects and stimulated adiponectin levels, which increases fatty acid combustion and energy dissipation, thereby ameliorating High fat diet-induced obesity and insulin resistance.

c) Enzymes of fat metabolism:

SCD1: Stearoyl- CoA desaturase-1 (SCD1) catalyzes the desaturation of long-chain fatty acids to generate monosaturated fatty acids, mainly oleic acid, for triglyceride and membrane lipid synthesis, and it is highly expressed in adipocytes as well as in liver [32]. The disruption in the SCD1 gene in mice [33] as well as naturally occurring inactivation mutation in the SCD1 gene (asebia) [34] results in mice that are resistant to diet-induced obesity and insulin resistance when fed a high-fat diet.

DGAT1: The enzyme microsomal acyl CoA diacylglycerolacyl transferase 1 known as (DGAT1) catalyzes the final and commited step in the glycerol phosphate pathway. Knockout mice lacking DGATI are resistant to diet- induced obesity and hepatic steatosis [35], seemingly as a result of an increase in energy expenditure and physical activity (Chen, 2006). As with the similar phenotype of the SCD1 knockout mice, DGAT1-deficient mice also have in increased insulin and leptin sensitivity.

11β-HSD1: The enzyme acyl CoA: diacyl glycerolacyltransferase 1(11β-HSD1) catalyzes the conversion of inactive cortisone to active cortisol in liver and adipose tissue. Mice lacking a functional 11β-HSD gene have been shown to be resistant to developing obesity and diabetes when put on a high-fat diet.

4.2 Treatment approaches to obesity:
The only evidence-based statements on diet composition included in the NIH (National Institute of Health) report relates to the amount of fat in the diet. This fact reflects the evidence supporting the suggestion that lower-fat diets (20% to 30% of calories) without doing targeted caloric reduction promote weight loss.

Table No. 1.3: Anti-obesity medications

Drug	Mechanism	Adverse effect	Status
Phentermine	Symathomimetic Amine (appetite suppressant)	Insomnia, tremor, ↑blood pressure and pulse rate, headache, palpitation, constipation	Currently approved drug for short-term weight management (≤ 12 weeks) in U.S., Korea and some countries, withdrawn 2000 in U.K.
Diethylpropion	As above	As above	Currently approved drug for short-term weight management
Zonisamide	Anti-convulsant agent	↑ Nervousness, sweating, tremors, gastrointestinal adverse effects, hypersomnia, fatigue and insomnia	Used off-label
Topiramate	As above	Paresthesia, dizziness, altered taste, fatigue, memory impairment, somnolence, anorexia and abdominal pain	Used off- label
Orlistat	Pancreatic lipase inhibition	Abdominal pain, bloating, flatulence,oily stools, diarrhoea	Only approved drug for long-term use in weight management

Decrease in energy intake and increase in energy consumed is the most important component of weight loss including optimum balance of greater than or equal to 55% carbohydrates of total energy intake, fat 20-30% of total energy, protein nearly 15% of total energy and fiber approximately 20-30 gm/day.

4.3 Surgical Treatment for Obesity:
Bariatric surgery had been used as a treatment for obesity over the last several years as the outcomes in obese persons with type 2 diabetes have been noted as impressive, the International Diabetes Federation has recently recommended consideration of bariatric surgery as an accepted treatment option in patients with a BMI of 30–35 kg/m^2 when diabetes cannot be adequately controlled by traditional medical management. [40] In 2011, LAP-BAND (gastric band) system was approved by FDA , to be used in patients who have not been successful in losing weight with a nonsurgical method and have a BMI of 30–34 kg/m^2 with comorbidity. This alternative of losing BMI without surgery and medications have been approved by many papers published in reputed and high class journals.

CONCLUSIONS

Obesity is an important public health problem in both developing and developed countries. It increases morbidity and mortality in different disease association both among children and adults and in both sexes. However strict diet control in relation to height and weight of the individual age, physical activity, less intake of chunk and high calorie food and increased consumption of vegetables, antioxidants, polyunsaturated fat will decrease the incidence of obesity. A social movement involving people of all niche like people representatives, government and private health organizations, mass media and each and every citizen of country could play a vital role to curb this menace. More molecular as well as long term studies can be carried out to discover new entities which have more therapeutic value as anti obesity medications as well as lesser side effects. Therefore, we should join hand in hand to fight for this fire like rising condition before it become an extreme curse for whole world.

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