

Obesity: An Introduction and Evaluation

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ABSTRACT:

Obesity is a pathological condition in with excess body fat. It is a chronic disorder with complex interaction between genetic and environmental factors. It is being characterized by high cholesterol, fatty acid levels, Insulin desensitization; high blood pressure; and excessive adipose mass accumulation. Currently more than 1 billion adults are overweight and at least 300 million of them are clinically obese. It is defined by body mass index and further evaluated by both percentage body fat and total body fat. Obesity is a risk to many secondary conditions like cardiovascular disorder, insulin pathological resistance, retinopathy, neuropathy and cancer. Various factors modulating the development of obesity are age, sex, smoking, growth hormone level, skeletal muscle metabolism. Experimental models used to evaluate obesity are high fat diet, high cafeteria diet, hypothalamic lesions, goldthioglucose induced obesity, monosodium glutamate induced obesity. Non-human primates, Spontaneously obese rats, Obesity due to natural allele defects in mice, V-Genetic variants in the human Uncoupled Protein-1 gene and Viral induce obesity are also preferred.

Keywords: Obesity, Mechanisms, Co-morbidities, Worldwide prevalence, Evaluation.

INTRODUCTION:

Obesity is a pathological condition in which excess body fat accumulated, leading adverse effects on health and life expectancy. [1] It is a chronic disorder with complex interaction between genetic and environmental factors. It characterized by high cholesterol, fatty acid levels; imbalance in metabolic energy; insulin desensitization; lethargy, gallstones; high blood pressure; shortness of breath; emotional and social problems; and excessive adipose mass accumulation with hyperplasia and hypertrophy. [2] Pathological obesity is associated with several secondary commodities like heart disease, type 2 diabetes, breathing difficulties during sleep, cancer and osteoarthritis.

[1] It is most commonly caused by a combination of excessive dietary calories, lack of physical activity, and genetic susceptibility. Evidence to support this view is that some obese people eat little yet gain weight due to slow metabolic rate. [3,4] The primary treatment for obesity are dieting and physical exercise. To supplement this, or in case of failure, anti-obesity drugs may be taken to reduce appetite or inhibit fat absorption. In severe cases, surgery is performed or an intragastric balloon is placed to reduce stomach volume and/or bowel length, leading to earlier satiation and reduced ability to absorb nutrients from food [5,6].

Worldwide prevalence:

Obesity is one of the leading preventable causes of death worldwide. [7] Currently more than 1 billion adults are overweight and at least 300 million of them are clinically obese. Current obesity levels range from below 5% in China, Japan and certain African nations, to over 75% in urban Samoa. Childhood obesity is already epidemic in some areas and on the rise in others. An estimated 17.6 million children under five yr. age are estimated to be overweight worldwide. According to the US Surgeon General, in the USA the number of overweight children has doubled and the number of overweight adolescents has trebled since 1980. The prevalence of obese children aged 6-to-11 years has more than doubled since the 1960s. Obesity prevalence in youths aged 12-17 has increased dramatically from 5% to 13% in boys and from 5% to 9% in girls between 1966-70 and 1988-91 in the USA. The problem is global and increasingly extends into the developing world: In Thailand the prevalence of obesity in 5-to-12 year olds children rose from 12.2% to 15-6% in just two years. Obesity accounts for 2-6% of total health care costs in several developed countries. The true costs are undoubtedly much greater as not all obesity-related conditions are included in the calculations. [8] In the United States obesity is estimated to cause an excess 111,909 to 365,000 death per year, while 1 million (7.7%) of deaths in the European Union are attributed to excess weight. [9,10]

Classification:

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health. [11] It is defined by body mass index (BMI) and further evaluated in terms of fat distribution via the waist-hip ratio and total cardiovascular risk factors. [12] BMI is closely related to both percentage body fat and total body fat. [13] In children a healthy weight varies with age and sex. Obesity in children and adolescents is defined not as an absolute number but in relation to a historical normal group, such that obesity is a BMI greater than the

95th percentile. The reference data that these percentiles are based on are from 1963 to 1994, and thus have not been affected by the recent increases in weight. [7,14,15]

BMI is calculated by dividing the subject's mass by the square of his or her height, typically expressed either in metric or US "customary" units) Metric: BMI = kilograms / meters²; US customary and imperial: BMI = lb *703 / in² where lb is the subject's weight in pounds and in is the subject's height in inches (Table 1).

The most commonly used definitions, established by the World Health Organization in 1997 and published in 2000 provide the values listed in the table at right. [2] The surgical literature breaks down "class III" obesity into further categories whose exact values are still disputed. [16] As Asian populations develop negative health consequences at a lower BMI than Caucasians, some nations have redefined obesity; the Japanese have defined obesity as any BMI greater than 25 [17] while China uses a BMI of greater than 28. [18]

Table 1: Classification of obesity based on BMI

BMI	Classification
< 18.5	underweight
18.5–24.9	normal weight
25.0–29.9	Overweight
30.0–34.9	class I obesity (Obese)
35.0–39.9	class II obesity (Sever obesity)
≥ 40.0	class III obesity (Morbid obesity)
≥ 40- 50	Super obese

Mechanisms:

Obesity is majorly responsible for metabolic dysfunction involving lipid and glucose. It also facilitates secondary complications like cardiac, liver, intestinal, pulmonary, endocrine, and reproductive dysfunctionings. The provoked inflammatory, insulin-resistant, hypertensive, and thrombotic-promoting adipokines, which are atherogenic are counter-balanced by anti-inflammatory and anti-atherogenic adipocyte hormones such as adiponectin, visfatin, and acylation-stimulating protein, whereas certain

actions of leptin and resistin are pro-atherogenic. [19] It occurs due to imbalance between food intake and energy expenditure. Possible involvement of NPY (Neuro Peptide Y), MCH (Melanocortin hormone), AGRP (Agouti gene related peptide), Orexin-A and -B, Galanin, α -MSH (α -Melanin stimulating hormone), CRF (corticotrophin releasing hormone), CART (caffeine and amphetamine releasing hormone), Glucagon-like peptide-1 (GLP-1), CCK (coli cysto kine), 5-HT (5-Hydroxy triptamine), insulin, and leptin found to occur during regulation of food intake. [20,21] Moreover, it also contributes to immune dysfunction from the effects of its inflammatory adipokine secretion; and the worsening of metabolic syndrome. Molecular and genetic studies of animal models have identified numerous genes that may cause or contribute to the development of obesity. They have also provided significant insight into the peripheral and central regulating cascades like (i) Peripheral: insulin, leptin, gheralin, CCK, 5- HT [20] and (ii) Central: NPY, AGRP, α -MSH, Orexin, CART, MCH [21] that control energy intake and expenditure. [Fig 1] Genetic studies of families and populations have generated useful information on genes and mutations associated with or linked to obesity, body fat distribution, and other relevant phenotypes. [22]

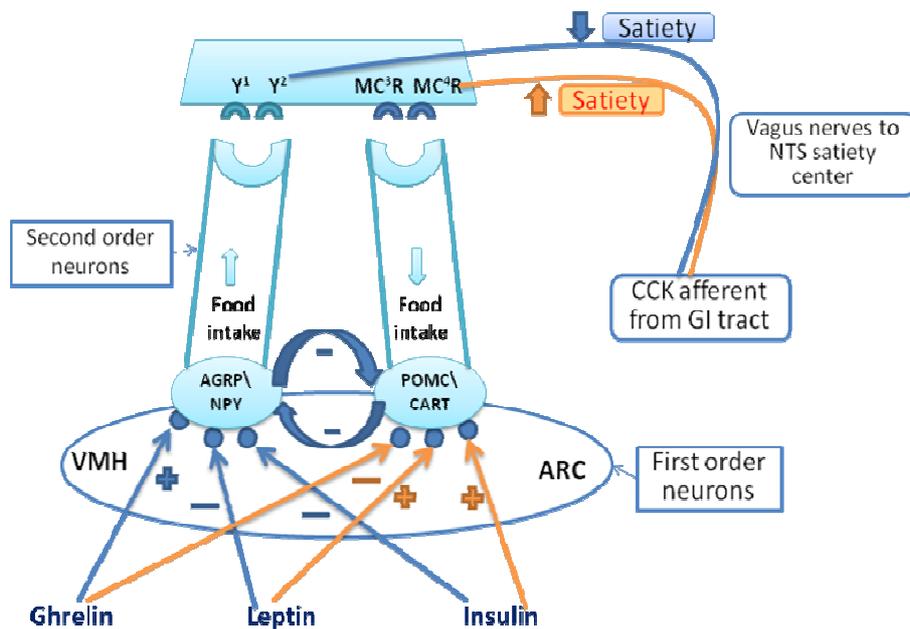


Figure : VMH (Ventral medial hypothalamus), ARC (Arcuate nucleus), NPY (Neuro peptide-Y), AGRP (Agouti gene related peptide), POMC (Propio melanocortin), CART (caffeine and amphetamine related peptide), CCK (Cholecystokines), GI (Gastro intestinal), Y1,2 (NPY 1,2 receptor), MC 3,4R (Melanocortin receptor)

Fig 1: Mechanism of Obesity

Co-morbidities associated with obesity:

Obesity increases the risk of several physical and mental conditions. The co-morbidities are most commonly shown in metabolic syndrome, which includes: diabetes mellitus (type 2), high blood pressure, high blood cholesterol, and high triglyceride levels. [23] Complications are either directly caused by obesity or indirectly related through mechanisms sharing a common cause such as a poor diet or a sedentary lifestyle. Excess body fat underlies 64% of cases of diabetes in men and 77% of cases in women. [24] Health consequences fall into two broad categories: those attributable to the effects of increased fat mass (such as osteoarthritis, obstructive sleep apnea, social stigmatization) and those due to the increased number of fat cells (diabetes, cancer, cardiovascular disease, non-alcoholic fatty liver disease). [24,25] Increases in body fat alter the body's response to insulin, potentially leading to insulin resistance. It also creates a pro-inflammatory state, Shoelson SE and a pro-thrombotic state. [24,26] Large-scale American and European studies have found that mortality risk is lowest at a BMI of 22.5–25 kg/m² in non-smokers and at 24–27 kg/m² in current smokers, with risk increasing along with changes in either direction. [27,28] The risk of obesity with higher co-morbidities are as follows.

- Cardiology - ischemic heart disease, angina and myocardial infarction, congestive heart failure, high blood pressure, abnormal cholesterol levels, deep vein thrombosis and pulmonary embolism. [1]
- Endocrinology - Diabetes mellitus, polycystic ovarian syndrome, menstrual disorders, infertility, complications during pregnancy, birth defects and intrauterine fetal death. [1]
- Neurology - Stroke, neuralgia parenthetical, migraines, carpal tunnel syndrome, dementia, idiopathic intracranial hypertension and multiple sclerosis. [29]
- Psychiatry - Depression in women and social stigmatization. [1]
- Rheumatology and Orthopaedics - Gout, poor mobility, osteoarthritis and low back pain. [30]
- Gastrointestinal – Gastroesophageal reflux disease, fatty liver disease and cholelithiasis (gallstones). [1]

- Respiriology - Obstructive sleep apnea, obesity hypoventilation syndrome, asthma and increased complications during general anesthesia [Fig 2]. [1]

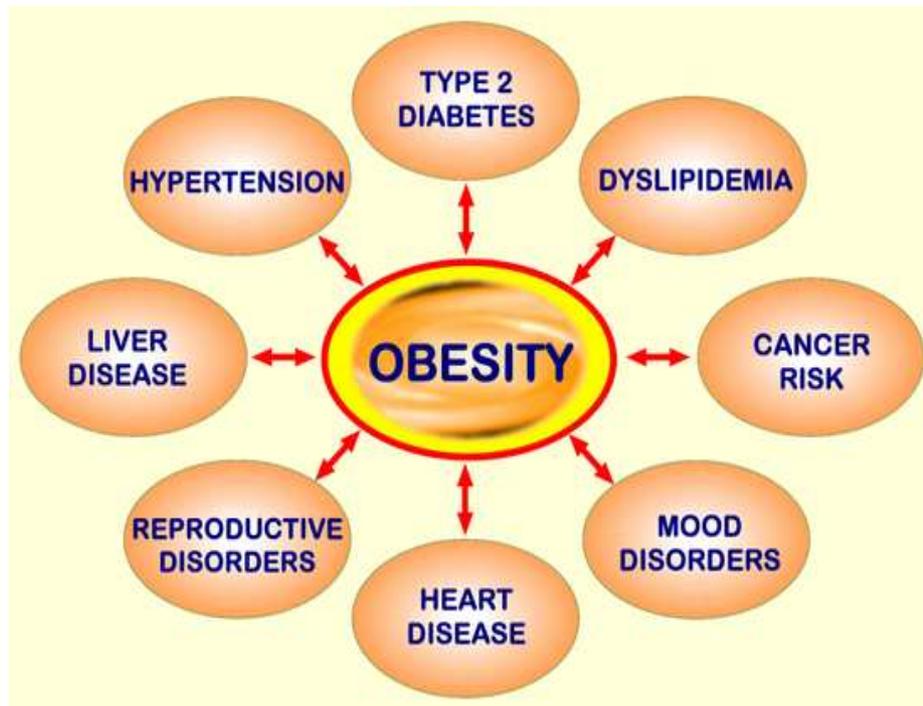


Fig 2: Co-Morbidities associated with Obesity

Factors modulating obesity:

Age - Childhood obesity is a risk factor for adulthood obesity, Body fat content increases during adulthood, the maximal rates of overweight and obesity attained from 55 to 65 yr. [31]

Sex - Women have more body fat. The differences in prevalence of obesity vary in populations or among ethnic groups. [31]

SES - More obese in high people SES (Socionomic status) classes and in poor countries, and obese in low SES classes and in rich countries. [31]

Energy intake - Overfeeding causes weight gain and leads to obesity. [31]

Dietary fat intake - Dietary fat is related to prevalence of overweight in ecologic studies. [31]

RMR - A low body mass and composition adjusted RMR (Resting metabolic rate) is a risk factor for weight gain, but some reports reveal that the, Overweight and obese people have higher absolute RMR. [31]

Physical activity (PA) level - A low level of PA is a risk factor for weight gain, Regular PA contributes to weight loss and weight maintenance. [31]

GH level - Low GH level is a risk factor for weight gain. [31]

Insulin sensitivity - Obese are often insulin resistant and hyperinsulinemic. [31]

Sex - Obese men often have low androgen levels, Obese women often have high androgen levels with further elevation on ACTH stimulation. [31]

Skeletal muscle (SM) metabolism - SM type I fibre type proportion is not affected by obesity, SM type IIb fibre type proportion is often elevated in obesity, SM oxidative enzyme markers are inversely related to obesity, SM LPL activity is low during obesity. [31]

Smoking: It attributol is associated with a lower body weight; Cessation increases body weight in most people. [31]

EVALUATION OF OBESITY

1. Diet induced obesity

Obesity can be induced in rats by offering a diet containing corn oil and condensed milk special diet contains Purina Rodent Chow, corn oil and condensed milk, resulting in a composition of 14.7% protein, 44.2% carbohydrate, 15.8% lipid, 2.5% fiber, 1.2% vitamin mixture, and 19% water. Body weight and food intakes are measured, and diet replaced, every 3 to 4 days. Obesity is developed in 2–3 months. [32]

2. Hypothalamic obesity

Hyperphagia in rats has been reported after hypothalamic lesions. [33,34] Due to the occurrence of hypothalamic lesions, the desensitization of leptin and insulin receptor present in the hypothalamus, takes place. Moreover, it is also attributed with the over expression of NPY and AGRP resulting excessive food intake and obesity. [28]

3. High Fat Diet

Lard or saturated oil added to diet takes 8 weeks to develop obesity most Commonly Used model HFD contains (32.6% Protein, 33% Fat , 30% Carbohydrate, Normal chow, Lard, Casein, cholesterol, Vitamins, minerals, Yeast powder, Methionine, Nacl). [35] The induction with HFD treatment causes increased free fatty acid, LDL, cholesterol, adipocyte differentiation.

4. Gold-thio-glucose induced obesity

Intraperitoneal or intramuscular injection of gold thio glucose induces obesity in mice. The effect is related to destruction of hypothalamic and extra-hypothalamic areas of the brain. [36]

5. Monosodium glutamate-induced obesity

Adiposity can be induced in mice by repeated subcutaneous injections of monosodium-L-glutamate at an early stage of life. [37]

6. Spontaneously obese rats

The occurrence of spontaneous obesity has been reported in several strains of rats. WBN/KOB RAT - Spontaneous hyperglycaemia, glucosuria and glucose intolerance have been observed in aged males of an inbred Wister strain, named the WBN/Kob rat. [38,39,40] These animals exhibit impaired glucose tolerance and glucosuria at 21 weeks of age. Obvious decreases in the number and size of islets are found already after 12 weeks of age. Fibrinous exudation and degeneration of pancreatic tissue are observed in the exocrine part, mainly around degenerated islets and pancreatic ducts in 16 weeks old males.

7. Obesity due to natural allele defects in mice

The 'new age' of obesity research seemingly began with the isolation of genes that cause spontaneous Mundelein obesity in mice. Most of the mouse monogenic obesity genes were discovered in mice with spontaneous mutations. More recently, investigators have used random mutagenesis [X-ray mutagenesis, chlorambucil, ethylnitrosourea (ENU)] to manipulate the mouse genome and thus search for obesity genes. X-ray mutagenesis and chlorambucil cause chromosomal rearrangements and deletions. In this model gene knock out, such as C57BL/6 (B6) for developing obesity. [11]

8. Non-human primates

Separation of the primate and rodent lineages is a relatively ancient event (65–85 million years ago). In contrast, the separation of the Hominoidea (humans and the other great apes) and the Cercopithecoidea (The Old World monkeys) occurred relatively recently (about 25 million years ago). So, Old World monkeys (such as macaques, rhesus monkey and baboons) may provide a genetically more appropriate model for studying human obesity. It has been demonstrated that 10–15% of captive macaque and rhesus monkeys develop age-related obesity when maintained on a relatively low-fat (10% of energy) ad libitum diet. [41] Interestingly, the reduced loco motor activity arising from caging appears not to be a key factor contributing to obesity in monkeys.

9. V-Genetic variants in the human UCP1 gene

The role of BAT and UCP1 in thermo genesis and body weight regulation has pointed to UCP1 as a candidate gene in the search for genetic variants and its relationship with some human obesity phenotypes. The human UCP1 gene was cloned, sequenced and mapped to the long arm of chromosome 4 (q31) (123), allowing identification of a first genetic variant of the UCP1 gene. A BclI polymorphic site was identified at bp –3826 upstream of the TATA box of the UCP1 promoter. This polymorphism resulted from an A(r)G point mutation. and Obesity in the result of UCP 1 gene mutation. [42]

10. Viral induced obesity

Canine distemper virus- Canine distemper virus is a morbillivirus and is antigenically related to measles. However, CDV primarily infects dogs and other wild mammals, not humans. [43] Experimental intracerebral injection of CDV produced enlarged fat cells, a twofold increase in body weight (63.7 ± 1.5 vs. 33.1 ± 0.8 g) and decreased levels of catecholamine among infected mice. No brain lesions were found. Did further studies on mice and CDV. They found that 30% of the infected mice had hyperinsulinemia, which was then followed by the development of obesity. It was also observed that viral particles had a tendency to accumulate in the hypothalamus, which controls hunger, among many other bodily functions. No significant changes in blood glucose levels were seen. However, leptin receptor expression levels were found to be decreased. Further, observed that there were decreased levels of prepro-melanin concentrating hormone precursor (ppMCH) mRNA, which is found to be involved in energy regulation, in all surviving obese mice. Decreased levels of ppMCH result in an increased food intake and/or a decreased energy expenditure. [34]

Adenovirus-37 and adenovirus-5- Two other human adenoviruses, Ad-37 and Ad-5, have been identified as causing obesity in chickens and mice. Ad-37 was shown to increase body fat and visceral fat in chickens. In contrast to Ad-36, Ad-37 did not reduce serum cholesterol levels; rather it increased serum cholesterol by 50% in infected chickens. The mechanism by which Ad-37 causes obesity is believed to be somewhat similar to how Ad-36 works in that it affects pre adipocyte differentiation. Infection with Ad-5 was found to increase body fat by 300% in infected mice compared with controls. Serum lipids were not measured in the study so there is no way of knowing how levels changed in response to infection. [44]

Borna disease virus- Borna disease virus, a non-segmented negative-stranded RNA virus, infects a broad range of warm-blooded animals from birds to primates. Infection causes movement and behavioral disturbances reminiscent of some neuropsychiatric syndromes. The virus has not been clearly linked to any human disease. However, an association between infection with the virus and selected neuropsychiatric disorders has been suggested. Gosztonyi and Ludwig first described obesity caused by BDV in rats. They observed inflammation of the hypothalamus, hyperplasia of pancreatic islets, and elevated glucose and triglyceride levels in infected rats. The development of obesity in BDV-infected rats depends on different factors such as age of infection, virus strain and rat strain. Later research done by comparative effects of different strains of BDV on obesity, they suggested that BDV causes obesity by damaging the hypothalamus with the accumulation of viral particles, which is similar to what is seen in the mechanism of CDV infection. [45]

CONCLUSION:

The review may conclude that the obesity is a multifactorial disease and it is characterized by extra fat accumulation, increased BMI. It is occurred due to imbalance in energy expenditure and food intake. The assessment can be done using fat diet, genetic and viral induced obesity models. Hence the evaluation and search of new therapeutic strategies are demanded to prevent this world wide co-morbidity.

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