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REVIEW ARTICLE

Obesity Therapeutics: A Global Problem that Needs Attention

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Abstract

Obesity is a multi-factorial disorder, which is associated with many important diseases such as diabetes mellitus, hypertension, other cardiovascular diseases, osteoarthritis and cancers. The management of obesity requires a comprehensive range of interventions which focuses on those people who have existing weight problems and also on those at high risk of developing obesity. Hence, prevention of obesity since early years of life should be considered a priority, as there is a risk of persistence to adulthood. This article highlights various preventive aspects and treatment procedures of obesity with special emphasis on the latest research trends in managing obesity.

Keywords: ***obesity, metabolic, genetic and environmental factors, energy.***

Introduction

Obesity is a disorder that affects millions of people in the entire world and is one of the causes for the development of diseases such as hypertension, neoplasm, cardiac disorders and diabetes mellitus.[1] Obesity is a chronic condition that involves an interaction between various environmental and genetic factors. It includes many derangements in the body such as elevated systemic blood pressures, elevated lipid levels, respiratory problems, high fatty acid levels, easy fatigability, decreased insulin sensitivity, social and emotional issues, excess adipose tissue accumulation, and cholelithiasis.[2]

It is the result of a positive energy balance in which energy intake is in excess of energy expenditure from the body that results in the storage of excess energy

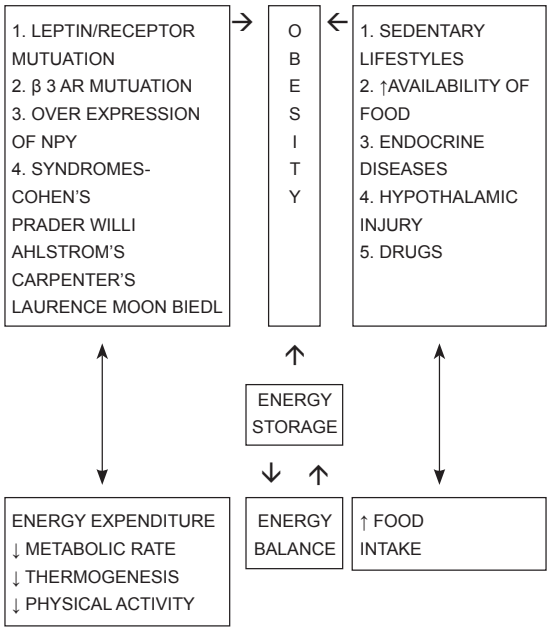
in the body as lipids in white adipocytes. Balance of energy in the body is maintained by intake of food and one's physical activity and also by the release of energy as heat by mode of constitutive thermogenesis in brown adipocytes in brown fat and also via inducible thermogenesis in beige adipocytes in white fat.[3–7] It is routinely caused by a lack of physical exertion, excess dietary intake of calories, and our genetic susceptibility pattern. This view is supported by the fact that some obese people eat less compared with others, but still they gain weight because their metabolic rate is slow.

Body mass index has a strong genetic influence with up to 80% heritability that involves multiple genes that have expression in the hypothalamus that have a role to play in our appetite regulation. The best association signal is present in introns 1 and 2 of the FTO gene.[8, 9] Obesity is one of the major preventable causes of death in the world. Nearly 3 million people die each year owing to their obese or overweight status.[10] Currently, it is estimated that the global prevalence of obesity has increased by twofold since 1980.[11]

Pathophysiology

Obesity is responsible for the derangement of metabolic function that involves glucose and lipids. It also helps in developing pulmonary, liver, intestinal, pulmonary, cardiac, endocrine, and reproductive complications. The stimulated adipokines, which are atherogenic in nature, are counterbalanced by anti-inflammatory and anti-atherogenic adipocyte hormones such as visfatin, adiponectin, and acylation-stimulating protein (ASP); in contrast, certain actions of leptin and resistin are pro-atherogenic in nature.[12] There is a possible involvement of neuropeptide Y, orexin-A, orexin-B, melanocortin hormone, agouti gene-related peptide, α-melanin-stimulating hormone, corticotrophin-releasing hormone, galanin, caffeine and amphetamine-releasing hormone, cholecystokinine, 5 hydroxytryptamine, insulin, glucagon-like peptide1, and leptin during regulation of food intake.[13,14] It also has a role to play in immune system dysfunction from the effects of its inflammatory adipokine secretion. Molecular and genetic studies of animal models have identified numerous genes that may cause or contribute to the development of obesity. 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.[15]

Etiology



Classification

Classification of obesity given by WHO:[16]

Classification	BMI (kg/m^2)	Chronic disease risk
Underweight	**<18.5**	Low (but increased mortality and morbidity from other causes)
Severe thinness	<16.0	
Moderate thinness	16.0–16.9	
Mild thinness	17.0–18.5	
Normal range	**18.5–24.9**	Average
Overweight	≥25.0	
Pre-obese	25.0–29.9	Increased
Obese	**≥30.0**	
Obese class I	30.0–34.9	Moderate
Obese class II	35.0–39.9	Severe
Obese class III	≥40.0	Very severe

Conditions associated with obesity

Obesity increases the risk of various mental and physical illnesses. The conditions that are most commonly associated are hypertension, diabetes mellitus, and elevated cholesterol levels in the body. 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 is present in 64% of cases of diabetes in men and 77% of cases in women.[17] Health consequences fall into two broad categories: those attributable to the effects of increased fat mass (such as osteoarthritis, obstructive sleep apnoea, and social stigmatisation) and those due to the increased number of fat cells (diabetes, cancer, cardiovascular disease, and non-alcoholic fatty liver disease).[17,18] Increased body fat alters the body's response to insulin, potentially leading to insulin resistance. It also creates a pro-inflammatory state and a prothrombotic state.[17, 19]

- Gastrointestinal tract – reflux oesophagitis, gall stones, and fatty liver.
- Heart and blood vessels –acute myocardial infarction, angina pectoris, ischaemic heart disease, congestive cardiac failure, deep vein thrombosis, dyslipidaemia, pulmonary embolism, and hypertension.
- Respiratory system –obesity hypo-ventilation syndrome, obstructive sleep apnoea, pulmonary hypertension, bronchial asthma, and increased incidence of respiratory complications during anaesthesia.
- Problems related with hormones and endocrine system– poly cystic ovarian syndrome, menstrual problems, increase in incidence of type 2 diabetes mellitus, infertility, pregnancy and labour complications, birth defects, intrauterine growth retardation, and intrauterine foetal death.
- Neurological problems –migraines, strokes, cerebrovascular accidents, carpal tunnel syndrome, tarsal tunnel syndrome, dementia, multiple sclerosis, and idiopathic intra cranial hypertension.
- Psycho-social problems – burden of social stigma and depressive disorders.
- Musculo skeletal issues – osteoarthritis, hyperuricemia, low back pain, muscle fatigue, and bone pain.

Investigations

History and physical examination

What to check	Comments
Height,weight, and BMI	We have to plot BMI on appropriate charts or calculate the *z* score
Waist circumference	Waist circumference can be quite useful for assessing the risk of co-morbidities associated with central obesity. However, the clinical advantage of change in waist over the period is not appreciable as it cannot be reproduced in clinical settings in real practice
Waist-hip ratio	The waist-hip ratio (WHR) is also used to measure obesity. It is measured by measuring the waist and the hip then dividing the waist measurement with hip
Blood pressure	Large exact-sized cuff needed for recording blood pressures as patients are overweight
Obstructive sleep apnoea	Whether the patient gives history of • Breathing problems during sleep • Snoring
Acanthosisnigricans	Thickened, velvety, hyper pigmented skin, acrochordon or skin tags that are mostly noticed around neck, arm pits, and in severe cases in all the flexure creases. This might be suggestive of insulin resistance
Obesity syndromes	Examine for difficulty in learning, retinitis, dysmorphic features in the body, early-onset obesity, hypogonadism, seizure disorder, and impaired hearing
History of any drug use	Steroids and anti-psychotics are most commonly linked with obesity

Hormonal and endocrine problems	Cushing syndrome can also be related to obesity that includes signs of short stature • stretch marks over skin • high blood pressure • hirsutism • telangiectasia • buffalo hump • irregular menstruation Hypo-functioning thyroid gland may be associated with obesity and may have features such as • hair changes • skin changes • short stature and goitre • slow motor functions • reduced or sluggish tendon reflexes
Dual energy X-ray absorptiometry (DEXA)	It is used to estimate fat-free mass, fat mass, and bone mineral density
Magnetic resonance imaging (MRI) scan	It is an accurate method to measure tissue, organ and whole-body fat mass as well as lean muscle mass and bone mass

Routine tests

A. Investigations for etiology	
Test	**Comment**
Thyroid function test	If there are no abnormalities on clinical examination, thyroid function tests are done

B. Investigations for associated conditions	
Test	**Comment**
Complete blood count, creatinine, blood urea, and electrolytes	Iron-deficiency anaemia may be seen in subjects with eating disorders
Lipid profile	Fasting sample should be taken to perform a full lipid profile and not just total cholesterol level
Fasting blood glucose and fasting serum insulin levels	HOMA INDEX (homeostatic model assessment) is a method to assess insulin resistance (IR) and beta cell function (β) HOMA-IR is calculated by the formula of glucose×insulin (mg/dl) 405 HOMA-B is calculated by the formula of 360×insulin (%) Glucose-63
Hepatic functions	Deranged liver function tests may suggest probable non-alcoholic fatty liver disease

Other tests

A. For etiology	
Test	**Comment**
Genetic studies	For syndromes related to obesity Offer to include in the Genetics of Obesity (GOOS) study, which is responsible for investigating monogenic causes of early-onset obesity
Calcium and phosphate levels	Rules out pseudohypoparathyroidism
Causes that lead to secondary obesity,for example, Cushing syndrome	Recent weight gain Height deceleration Elevated blood pressure Hirsutism Acne

B. For associated conditions	
Test	**Comment**
Sleep studies	To detect obstructive sleep apnoea and other sleep problems associated with obesity
For polycystic ovarian syndrome	1. Pelvic ultrasound 2. Blood for • FSH and LH • 17 hydroxy-progesterone • Adrenal androgens (androstenedione, dehydro-epiandrosterone sulphate, testosterone • Prolactin • Sex hormone-binding globulin
Oral glucose tolerance test	Following subjects should be considered: 1. Having extreme obesity 2. BMI ≥ 98th percentile and has ≥2 of the following: • Family history of type 2 diabetes • Clinical signs of insulin resistance syndrome (Acanthosis nigricans, hypertension) • Ethnicity (Middle-Eastern, Hispanic, South Asian, black African) • Evidence of the insulin resistance (hyperinsulinaemia, dyslipidaemia on fasting sample) • Signs and symptoms of polycystic ovarian syndrome The most useful protocol would measure glucose and insulin every 30 min. If this is not possible, the priority values are the 0 and 120 min glucose and the 0 and 60 min insulin

Management of obesity

Obesity is a chronic disorder that is difficult to manage. Unless fat is surgically removed (e.g. liposuction), the only way to lose fat is through negative energy balance. Theoretically, this can be achieved by reduced food intake, increased physical activity, or a combination of these. Here is the summary of the treatment options for obesity:

Non-pharmacological approach

- **Dietary management and physical activity**

Use of behaviour therapy to help patients adopt necessary life style changes is necessary in the treatment of obesity. There are various diet plans that give emphasis on certain nutrients such as low carbohydrate diets, low fat diets, high protein diets, and diets with low glycaemic index. However, diet constitution is of less importance than total amount of calories consumed by a person. This significantly depends on the ability and will of a person to stick to their diet plan. A meta-analysis shows that the effect of counselling about significance of a diet plan is not that much, which shows a decrease of 0.1 BMI units per month and later regain during the maintenance phase.[20] Physical activity alone has got a little effect on body weight. Addition of exercise to a diet plan increases the chances of an effective weight reduction programme.[20,21] Even slight increase in our physical activity can have positive outcomes on our cardiac and pulmonary functions and fitness,and these factors can reduce many adverse effects of obesity and its related conditions.

- **Very low calorie diets**

A very low calorie diet (VLCD) is defined as a diet that has an calorie content of not more than 800 kcal/day and which has ample quantities of proteins, essential fatty acids, carbohydrates, and the recommended daily allowances of vitamins and minerals.[22] Regular foods are replaced by up to five VLCD meals along with up to 2.5 L of water per day. And at the completion of the VLCD period, regular food is gradually introduced again over the period of up to 4 weeks. In some programs, VLCD is often used up to 16 weeks, which results in average reduction in the person's weight of about 1.5–2.5 kg/week.[22,23] VLCDs are primarily indicated in obese patients who have associated risk factors that can benefit from good weight loss like diabetes mellitus (type 2) and also where rapid weight reduction is desired before a surgery. Sometimes, there are chances of rebound increase in weight after stopping VLCD; therefore, VLCD should be managed by aggressive weight management programme to maintain the effect.

Pharmacological Approach

1. Appetite Suppressors

Mechanism of action	Examples	Adverse effects	Contraindications
Nor-epinephrine release inhibitors	Phendimetrazine Benzphetamine	Dry mouth, insomnia, constipation, palpitations, hypertension, euphoria, dependence	Hyperthyroidism, cardiovascular disorders, hypertension, glaucoma, abuse, agitation
Serotonin re-uptake inhibitors	Fenfluramine Dexfenfluramine	Pulmonary hypertension and valvular heart disease	Both withdrawn from the global market in 1997
	Lorcaserin	Highly selective for the 5 HT2c receptor compared with 5 HT2b receptor (less chances of valvulopathies)	
Nor epinephrine and serotonin re-uptake inhibitors	Sibutramine Phentermine (Sibutramine withdrawn in the year 2010) Phentermine + topiramate combination (topiramate appetite-reducing mechanism is not thoroughly understood although it may be through its effect on GABA receptors)	Dry mouth, constipation, increased heart rate, insomnia, elevated blood pressure, and headache	Severe hypertension, congestive cardiac failure, history of arrhythmias, history of stroke, ischaemic heart disease, history of drug abuse, glaucoma, and renal and hepatic impairment

2. Inhibitors of fat absorption

Mechanism of Action	Examples	Adverse Effects
Binds gastric and intestinal lipases (lipase inhibitors)	Orlistat Cetilistat	Decreased absorption of fat-soluble vitamins and gastrointestinal disturbances

3. Other drugs

Drug	Mechanism of action	Example
Thermogenesis stimulators	Beta 3 adrenergic receptor agonists	SWR-0342SA
Drugs that stimulates fat mobilisation	Stimulates formation of brown adipose tissue	PPARγ ligands, PCG1
Cannabinoid receptor 1 antagonist (withdrawn in 2009)	Decrease appetite and increases thermogenesis	Rimonabant Taranabant Side effects –severe mood disorders
Other drugs	Activates leptin pathway, inhibits activity of acetyl coenzyme A carboxylase	Axokine (ciliaryneurotrophicfactor)
Liraglutide	Selective glucagon-like peptide-1 (GLP-1) receptor agonist	Approved in January 2010
Naltrexone + Bupropion combination	Naltrexone is a pure opioid antagonist Bupropion is a reuptake inhibitor of nor-epinephrine. It is also acetyl choline nicotinic receptor antagonist. It activates pro-opiomelanocortin (POMC) neurons in hypothalamic region,which results in decreased appetite and increased energy output	Approved by the US-FDA in 2014

4. Calorie Restriction Mimetic

Most commonly studied drug in this category is resveratrol, which is a plant-based polyphenol produced in a response to attacking pathogens. It is derived from the skin of red grapes, from a Japanese weed known as Fallopia japonica, red wine, mulberry, and peanuts. It has shown to have anti-ageing properties demonstrated in certain flies and yeasts. The molecular pathway responsible for calorie restriction in yeast requires activation of the silent information regulator 2 (Sir 2) gene.[24, 25] The mechanism of action of resveratrol is based on its capability to mimic the calorie restriction in a Sir 2-dependent manner. The corresponding Sir 2 genes in humans are known as SIRTs (1–7), which are expressed in nucleus, cytoplasm, and mitochondria of human cells, and on activation,these SIRTs in humans result in insulin secretion, mobilisation of fat, and gluconeogenesis.[26–28]

Second in line in group of CRM are insulin sensitizers such as metformin, which is a commonly used anti-diabetic drug for type 2 diabetes mellitus. Metformin increases sensitivity of insulin receptors, but it does not increase the secretion of insulin, and it is also known to suppress glucose synthesis, and its inhibitory effect depends on the AMP-activated protein kinase (AMPK). It has been shown that the treatment with metformin for couple of months has a significant impact on the outcome of long-term calorie restriction in mice.[29]

The third group of CRM includes thiazolidinediones such aspioglitazone and rosiglitazone. Thiazolidinediones increase the sensitivity of the cell to insulin by activation of the nuclear receptor PPARγ. However, studies have shown that thiazolidinediones has increased risk of death from cardiovascular causes.[30]

Surgical treatment

1. Bariatric surgery

Obesity surgeries such as gastric banding, gastric bypass, and vertical-banded gastroplasty provide the greatest degree of sustained weight loss for severely obese patients. Surgical management of obesity results in 20–40 kg of weight loss and a 10–15 kg/m^2 reduction in BMI.[31, 32] This treatment is usually reserved for adult patients if they have a BMI >40 kg/m^2 or >35 kg/m^2 with serious co-morbid associated conditions.[3]

2. Prevention of obesity

To maintain a healthy weight, one should reduce the intake of high calorie foods and select a low fat and high fibre-containing diet; consume less fast food; eat more fruits, whole grains, vegetables, and salads; minimise alcohol intake; and consume less confectionery and sugared drinks. International consensus guidelines, which are based on data from epidemiological prospective studies using physical activity estimates obtained through questionnaires, recommend that adults should engage in 45–60 min of moderate intensity physical activity per day to prevent the transition to overweight or obesity.

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