An overview on Obesity

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Abstract

Obesity is a condition where BMI is ≥30kg/m². Obesity is seen to raise alarmingly due to the imbalance between the calorie intake and calorie expenditure. USA, China, India, Brazil are among the top 10 obese countries as of 2017. Obesity is caused due to physical, environmental and psychological factors affecting the body. Risk factors include changes in lifestyle, urbanisation which led to decrease in physical activity. Hypertrophic and Hyperplastic obesity are the two types of obesity patterns. Pathophysiology of obesity is characterised by the chronic and low-grade inflammation of an adipocytes due to the activation of inflammatory signalling pathway. Body Mass Index, waist-to-hip circumference ratio, waist circumference are the diagnostic parameters of obesity. Obesity can be treated initially with non-pharmacological treatment where diet restriction, regular physical activity and lifestyle modifications can be done. Pharmacological treatment includes use of appetite suppressants and lipase inhibitors class of drugs. Pharmacist can play a vital role in educating people and creating awareness about complications of obesity.

Keywords: Obesity, Non-pharmacological treatment, macrophages, Appetite suppressants.

Introduction

Obesity has emerged as one of the most serious health concerns in the present generation. Obesity is mainly due to the imbalance between the energy intake and energy expenditure[1]. In general, obesity refers to the condition where abnormal high proportions of the fat are present in the body and it also conveys the significant risk for other adverse health issues like cardiovascular events, insulin resistance etc. The assessment and management of obesity is affected by both the endogenous and exogenous factors[2]. It is estimated that for every 1Kg raise in body weight above the normal body weight the prevalence of diabetes mellitus raises by 9% [5].

Definition

According to the World Health Organization, obesity is defined as Body Mass Index (BMI) ≥ 30 kg/m² and central obesity as a waist circumference greater than 102 cm in men and 88 cm in women[3]. Whereas children whose BMI exceeds the 95th percentile value are considered as obese[4].
Epidemiology

The prevalence of obesity is seen to raise alarmingly and is now worldwide epidemic[1]. According to WHO, obesity has increased rapidly from onset of last decades of 1900. Worldwide prevalence of obesity has raised during 1980 and 2008. In 2008 approximately 35% of adults were overweight with BMI > or equal to 25kg/m²-29kg/m² among which 34% were men and 35% were women. In 1980 5% of men and 8% of women were found to be obese whereas this rate has increased to 10% of men and 14% of women in 2008. More than half a billion adults over the age of 20 worldwide were found to be obese[1]. In 2015, 19.5% of population was obese worldwide with less than 6% in Korea, Japan and 30% in Hungary, New Zealand, Mexico and USA. More than 1 in 4 adults is obese in Australia, Canada, South Africa and United Kingdom. Prevalence of obesity has increased over the past decade in Canada, France Mexico, Switzerland and USA comparatively the rate was stabilised in England, Italy, Korea and Spain[6]. Female obesity is higher than male obesity for all categories of income countries, except in the case of high-income countries where male obesity (21.8%) is slightly more elevated than female obesity (21.6%) as they prefer a leaner body image and hence engage themselves in higher physical activity to remain fit[7].

In 2000, International Obesity Task Force (IOTF) declared 10% of children aged between 5 to 17 years were overweight accounting for about 155 million globally and among them 2% to 3% were obese[8]. It has been projected that by the year 2030 levels of obesity could be as high as 50-80% in the USA, between 30-40% in Australia, England and Mauritius and over 20% in some developing countries[8]. The top 10 countries contribute half the entire world’s obesity.

Of the total world population (7,505,257,673), approximately 10.5% population is obese (774,000,000).

Table-I Top 10 most obese countries in the world-2017[9]

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the Country</th>
<th>Obese population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>United States of America</td>
<td>109,342,839</td>
</tr>
<tr>
<td>2.</td>
<td>China</td>
<td>97,256,700</td>
</tr>
<tr>
<td>3.</td>
<td>India</td>
<td>65,619,826</td>
</tr>
<tr>
<td>4.</td>
<td>Brazil</td>
<td>41,857,656</td>
</tr>
<tr>
<td>5.</td>
<td>Mexico</td>
<td>36,294,881</td>
</tr>
<tr>
<td>6.</td>
<td>Russia</td>
<td>34,701,531</td>
</tr>
<tr>
<td>7.</td>
<td>Egypt</td>
<td>28,192,861</td>
</tr>
<tr>
<td>8.</td>
<td>Turkey</td>
<td>23,819,781</td>
</tr>
<tr>
<td>9.</td>
<td>Iran</td>
<td>21,183,488</td>
</tr>
<tr>
<td>10.</td>
<td>Nigeria</td>
<td>20,997,494</td>
</tr>
</tbody>
</table>

Etiology

Genetic factors play an important role in the regulation of body weight. It is estimated that genetic factors account for 50% to 90% of the variability in BMI than all the other factors but the WHO Consultation on Obesity concluded that behavioural and environmental factors are primarily responsible for the rapid increase in obesity during the past two decades[1]. Therefore, the current obesity epidemic not only depends on the genetical factors but are also the result of environmental and behavioural factors interacting with genetic factors[1].

The psychological disorders like depression, anxiety, stress, maniac conditions can affect the consumption of food[2]. The behavioural factors include frequent fast food consumption, large portion sizes, high consumption of beverages high in sugar, disruption of the circadian system of an individual due to shift work, late night consumption of food and breakfast omission. The Environmental factors include proximity of large supermarkets, the concentration of fast food establishments and restaurants[10].

Risk Factors

Risk factors associated with obesity are similar to the etiological factors, which include in sufficient sleep and circadian misalignment are novel, modifiable risk factors for the development of obesity[11]. Rapid changes in lifestyle, urbanisation, change in food processing, high
adiposity is negatively correlated with production of adiponectin (also known as ACRP30), a hormone which decreases hepatic gluconeogenesis and increases lipid oxidation in muscle\(^{12}\). Total numbers of T cells, B cells, macrophages, neutrophils, and mast cells are increased in visceral adipose tissue of obese individuals. In contrast, the number of eosinophils and specific subsets of T cells like —T-helper type 2 cells, regulatory T-cells remain constant or decreased in the obese adipose tissue.

In obese conditions, adipocytes begin to secrete low levels of TNF-\(\alpha\), which can stimulate preadipocytes to produce monocyte chemotactant protein-1 (MCP-1). Similarly, endothelial cells also secrete MCP-1 in response to cytokines, attracting macrophages to adipose tissue\(^{12}\). Increased secretion of leptin or decreased production of adiponectin by adipocytes also contribute to macrophage accumulation to adipose tissue and promotes the adhesion of macrophages to endothelial cells which causes size changes, crowding or oxidative damage that results in an increased lipolytic environment. If once these cells are activated along with adipocytes and other cell types, could perpetuate a vicious cycle of macrophage recruitment, production of inflammatory cytokines, and impairment of adipocyte function.

**Diagnosis**

The three simple measures that are widely used in the diagnosis of obesity in clinical practice are:

1. **Waist circumference**
2. **Waist-to-hip circumference ratio (WHR).**
3. **Body Mass Index (BMI)**
4. **Waist-to-weight ratio (WHtR)**

**Waist Circumference**

Waist circumference (WC) and waist-to-hip ratio (WHR) are the anthropometric factors used for the diagnosis of central obesity.

The Waist circumference can be measured by using a stretch resistant tape which provides a constant tension of 100g\(^{15}\). The measurement should be done from the midpoint between the

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lower margin of the least palpable rib and the top of the iliac crest while the subject is positioned to stand with arms at the sides, feet positioned close together, and weight evenly distributed across the feet. The waist circumference is usually measured at the end of a normal expiration. Care should be taken that the subject is allowed to take a few deep, natural breaths before the measuring procedure to avoid the inward pull of an abdominal wall as it affects the accuracy of measurement.

Table 2 Boundary values for Waist circumference

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Gender</th>
<th>Low</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Men</td>
<td>≤ 94 cm</td>
<td>94-102cm</td>
<td>≥ 102cm</td>
</tr>
<tr>
<td>2.</td>
<td>Women</td>
<td>≤80cm</td>
<td>80-88cm</td>
<td>≥88cm</td>
</tr>
</tbody>
</table>

Body Mass Index

The body mass index (BMI) is used for defining anthropometric height/weight characteristics in adults and for classifying them into groups. The BMI does not provide information about the mass of fat in different body sites[16]. The WHO assembled an Expert Consultation Group in 1993 with a charge of developing uniform categories of the BMI which are similar to those suggested by John. S and Garrow in 1981[16]. The results were published as a technical report in 1995. According to this report, four different categories were established:

- Underweight- 15-19.9
- Normal- 20-24.9
- Overweight- 25-29.9
- Obese- 30-35 or greater

A BMI of 16.9 in men and 13.7 in women represents a complete absence of body fat stores. In 1997, the International Obesity Task Force expanded the number of BMI categories to include different degrees of obesity and changed the different categories.

IOTF classification of BMI categories:

Table 3 Categories of BMI[16]

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Category of BMI</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Underweight</td>
<td>15-19.9</td>
</tr>
<tr>
<td>2.</td>
<td>Normal weight</td>
<td>20-24.9</td>
</tr>
<tr>
<td>3.</td>
<td>Overweight</td>
<td>25-29.9</td>
</tr>
<tr>
<td>4.</td>
<td>Class I obesity</td>
<td>30-34.9</td>
</tr>
<tr>
<td>5.</td>
<td>Class II obesity</td>
<td>35-39.9</td>
</tr>
<tr>
<td>6.</td>
<td>Class III obesity</td>
<td>≥40</td>
</tr>
</tbody>
</table>

Treatment

The strategies involved in the treatment of obesity include both non-pharmacological and pharmacological treatment. Non-pharmacological treatment include lifestyle modification, dietary modifications and increased physical activity. The pharmacological treatment includes the use of different drugs and the surgical procedures if required.

Table 4 Algorithm for an assessment and step-wise management of overweight and obese adults[17]

1. Determine the degree of overweight or obesity. If BMI ≥ 25kg/m² or waist circumference ≥ 94 cm (men) and ≥ 88 cm (women).
2. Assess the presenting symptoms, underlying causes, complications along with lifestyle, diet, physical activity, eating behaviour and other psychological factors like depression and mood disorders.
3. Set weight loss goal- 5 to 12% of body weight or 0.5 to 1 kg per week.
4. Propose realistic, individualised and long-term aimed lifestyle modifications.
5. The intensity of intervention depends on the level of risk and the potential to gain the health benefits. Nutrition: Reduce energy intake by 500-1000 kcal/day, physical activity of about 30 min for 3-4 days a week initially which can be increased to 60 min on most days of the week. Pharmacotherapy is required if BMI ≥ 30kg/m² (trick factors in use of diet and lifestyle modifications. Brian surgery is required if BMI ≥ 40kg/m², trick factors if other weight loss attempts have failed.
Non-Pharmacological Treatment
The non-pharmacological treatment of obesity include dietary and lifestyle modifications.

Dietary Modifications
The goals of Dietary modifications involve reducing and stabilizing caloric intake, reducing fat intake, and restructuring eating habits resulting in increased nutrient density\textsuperscript{18}. It shows great outcomes when the patient is advised to maintain a self-recorded chart to note the intake of daily calories. Dietary modifications should encourage healthy eating food like grains, cereals, fibre, vegetables and fruits to substitute low-fat dairy products and meat rather than focussing on the consumption of low quantity of food.

In some patients with overweight (BMI 25.0–29.9 kg/m\textsuperscript{2}) prevention of further weight gain through increased physical activity should be focussed rather than weight loss and may be appropriate target. The weight loss programmes should be realistic, individualised and should aim for long term affects.

Practical weight loss objectives are: –
1. 5–15\% weight loss over a period of 6 months is realistic and of proven health benefit.
2. 20\% or more weight loss can be appropriate for the people with (BMI \geq 35 kg/m\textsuperscript{2})\textsuperscript{17}.

Maintenance of weight loss and prevention and treatment of co-morbidities are the two main criteria for success.

The traffic-light diet, categorizes food into three types:

i. Green Food: Food items under this category can be consumed without any limit.

ii. Yellow Food: They should be consumed under caution as they have average nutritional values.

iii. Red Food: Most of these food items should be avoided as they provide less nutrient density per calorie because of high fat or simple carbohydrate content\textsuperscript{18}.

The Traffic-light diet (900-1300 kcal) provides an increased nutrient density for calcium, iron, proteins, thiamine, riboflavin, vitamin A and a decreased nutrient density for fat in preadolescents. In addition to short-term effects, long-term obesity changes extending from 5 to 10 years have been observed with the traffic-light diet in combination with behavioural, exercise and familial components. Some studies suggest that replacing two of three meals with a liquid and/or solid meal replacement or at least two meals with a portion-controlled entry resulted in greater weight loss than self-selected diets\textsuperscript{19}.

Hypocaloric balanced diets (HBD) or balanced deficit diets consists of diets that provide 1,200 kcal/day\textsuperscript{17}. The Very Low Calorie Diets (VLCD) are the diets which provide (less than 800 kcal/day) may form a part of vigorous diet management. This dietary management results in 15\% to 20\% of reduction in weight in 3 to 6 months. The long term results include 9\% weight reduction about 1 year and 5\% weight reduction after 4 years. However the VLCD should be limited for short duration of time and for specific patients like children, adolescents, pregnant or lactating women and elderly as it is unsuitable as a sole source of energy\textsuperscript{17}.

Behavioural Treatment
The Behavioural treatment can be considered as an approach to help individuals to develop positive skills towards reducing the weight and to maintain a healthy weight. It helps the patient to identify the triggering factor for excess eating when followed on regular basis. Cognitive therapy is also a part of behavioural therapy\textsuperscript{19}. CBT helps an individual to change their negative eating behaviours and follow healthy lifestyle changes\textsuperscript{10}. Behavioural treatment is always goal oriented and provides a set of goals to the patient. The behavioural treatment includes the changes in food habits, physical activity, problem solving capacity.
Pharmacological Treatment
The pharmacological treatment is generally prescribed to the patient if the desirable results are not achieved by the non-pharmacological treatment\footnote{1}. Now-a-days drug therapy is prescribed to the patients with a BMI ≥ 30 kg/m² or a BMI ≥ 25 kg/m² along with an obesity-related morbidities\footnote{20}. The drugs which are used for the treatment of obesity can be divided into two categories Appetite suppressants and lipase inhibitors\footnote{21}. The therapy should be discontinued if the desirable results are not achieved after the 3 months of initiation of therapy. Reduction in >5% weight loss in non-diabetic and >3% in diabetic patients is considered to be the satisfactory results. Dinitrophenol in 1933, amphetamine in 1937, pills containing digitalis and diuretics in 1967 were discovered and are discontinued due to their side effects. In 1971 a new appetite suppressants aminorex, or aminoxaphen, were discontinued or banned in Europe due to an outbreak of pulmonary hypertension. Later the combination therapy of fenfluramine and phentermine are used but due to their side effects like valvular insufficiency these drugs were also discontinued\footnote{22}.

The drugs used for the treatment of obesity include:

**I. Appetite Suppressants**
Ex: Sibutramin, fluoxetine, sertraline, phentermine, diethylpropion, zonisamide, topiramate.

**II Lipase Inhibitors**
Ex: Orlistat

**III Others**
Ex. Lorcaserin, Naltrexone and bupropion, Liraglutide

1. **Phentermine**
It is a sympathomimetic amine\footnote{21}. Side effects include palpitations, tachycardia, elevation of blood pressure, central nervous system effects, and gastrointestinal effects\footnote{13}. It acts by stimulating neurons to release or maintain high levels of catecholamines like dopamine and norepinephrine which suppress hunger signals and appetite. It also inhibit reuptake of noradrenaline, dopamine, and serotonin through inhibition of the reuptake transporters. Phenterminemay also indirectly affect leptin levels in the brain which signal satiety.

**Dose:** 15 mg or 37.5 mg orally once daily; 8 mg orally 2–3 times daily; can start with a quarter or a half of a 37.5 mg tablet once daily up to a maximum dosage of 37.5 mg\footnote{13}.

2. **Phenteramine/Topiramate**
It is a combination of sympathomimetic amine, anorectic and ER antiepileptic drug. The total percentage of weight lost in the topiramate-treated patients was 8%, and there was significant heterogeneity among. It acts by blocking voltage mediated sodium gates in the central nervous system and prevents repeated stimulation of neurons. Side effects include Paraesthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth\footnote{13}.

**Dose:** It is taken once daily in the morning with or without food. Start with3.75/23 mg orally once daily for 14 days; increase to 7/46 mg once daily and monthly to achieve weight loss; discontinue if <3% weight loss on 11.25/69 mg or <5% weight loss on maximum dose of 15/92 mg after 12 weeks\footnote{13}.

3. **Orlistat**
It is a gastrointestinal lipase inhibitor. Side effects include Oily Spotting, Flatus with Discharge, Fatty/Oily Stool, fecal incontinence\footnote{13}. Orlistat acts by binding covalently to the active site on pancreatic lipase and forms a stable complex which conformational change in the enzyme results in exposing the catalytic active site. It leads to acylation of a hydroxyl group on serine residue burden on the active site of the enzyme making it inactive as lipase. Due to the inactivation of lipase, fats are not hydrolysed in to fatty acids and monoglycerides and are excreted in the faeces.

**Dose:** 120 mg capsule thrice a day.
4. **Lorcaserin**

Lorcaserin is 5-HT2C receptor agonist. It acts by selectively activating the 5-HT2C receptors which results in satiety. Side effects include Hypoglycaemia, headache, back pain, cough, fatigue, dry mouth, constipation\(^{[13]}\).

**Dose:** 10mg PO for q12 hrs or 20mg PO for qday\(^{[23]}\).

5. **Naltrexone SR / Bupropion**

Bupropion and naltrexone act in a synergistic manner on the central neural pathways within the hypothalamic arcuate nucleus to reduce appetite and increase energy expenditure. Bupropion is an aminoketone and acts inhibiting the reuptake of both noradrenalin and dopamine. Naltrexone is an opioid antagonist and along with its active metabolite 6-b-naltrexol function as competitive antagonists at µ- and k-opioid receptors. Side effects include difficulty in sleeping, anxiety, nervousness, abdominal pain or cramps, nausea, vomiting, low energy, joint and muscle pain, and headache\(^{[13]}\).

**Dose:** In week 1, one 8/90-mg tablet once a day in the morning. In week 2, increase the daily dosage to one tablet in the morning and other in the evening. During week 3, increase the daily dosage to two tablets in the morning and one tablet in the evening, and in week 4, two tablets twice a day\(^{[24]}\).

6 **Liraglutide**

Liraglutide is a glucagon like peptide-1 (GLP-1) receptor agonist. Liraglutide 3mg daily subcutaneous injection is the newest (2014) FDA approved drug for chronic weight management in patients with a BMI ≥27 kg/m\(^2\) and comorbid condition. Side effects include nausea, vomiting, diarrhoea\(^{[13]}\).

**Surgical Treatment of Obesity**

Surgical treatment of obesity is also referred to as Bariatric surgery. The surgical procedures involved in the treatment of obesity can be divided into two types\(^{[25]}\):

- **Malabsorptive procedures**
- **Restrictive procedures**

The decrease in the absorption of nutrients by shortening the functional portion of small intestine is done in malabsorptive procedures. Biliopancreatic diversion with duodenal switch and Biliopancreatic diversion are the two malabsorptive procedures which are currently in use. In both procedures, a 100–150ml gastric pouch is created by performing partial gastrectomy. The biliopancreatic diversion consists of a horizontal distal gastrectomy with a gastro-jejunostomy or gastroileostomy. In a biliopancreatic diversion with duodenal switch, apylorus-sparing sleeve gastrectomy with duodeno-ileoostomy is performed.

In restrictive operations the storage capacity of the stomach is reduced which causes early satiety leading to the lower calorie intake. The most frequently performed restrictive procedures are:

- **Vertical banded gastroplasty**
- **Laparoscopic adjustable gastric band**

In vertical banded gastroplasty, a small pouch of 30 ml, and a narrow outlet of 11mm is created and re-inforced by Marlex mesh\(^{[26]}\). The laparoscopic adjustable gastric band technique involves placing an inflatable silicon gastric band horizontally around the proximal part of the stomach. By inflating the gastric band via as.c. port, a pouch is created\(^{[25]}\). Now-a-days, the Roux-en-Y gastric bypass is the most frequently performed bariatric procedure as it includes both restrictive and malabsorptive aspects. A restrictive part of the procedure includes creating a gastric pouch and separating it from the remaining part of the stomach. The continuity is then restored by a Roux-Y-limb, which is connected to the jejunum. During an intake of food, the gastric pouch gets filled quickly creating a sensation of satiety. Food in the gastric pouch enters the jejunum via the Roux-Y-limb. The reduction in the length of the common limb leads to malabsorption of the nutrients\(^{[25]}\).

**Complications in Bariatric Surgery**

Though bariatric surgery is one of the important treatment option for people with extreme obesity...
it involves many complications and risk associated with it. The severity of the complications depends on the procedure involved. The complications can be classified as perioperative complications, immediate post operative complications, late complications[27].

1. **Peri and Post Operative Complications**
   These complications include Fistula or leaks, intestinal obstruction and internal hernia, bleeding, strictures, wound infection, pulmonary embolism, anastomotic ulcer, rhabdomyolysis, abdominal wall complications.

2. **Late Complications**
   These complications include nutritional deficiencies, cholelithiasis and complications specific to gastric banding.

**Role of Pharmacist**
A clinical pharmacist plays an important role in treating obesity as most of the initial step in treating obesity is Non-pharmacological treatment. Dietary modifications, lifestyle modifications, engaging in regular physical activities can be followed effectively with an intervention of a pharmacist. By patient counselling, the assessment of patient’s psychological issues can also be done which may be the risk factor of obesity. If the patient is not treated with non-pharmacological treatment, clinical pharmacist can discuss other options such as pharmacological treatment and bariatric surgeries. Patient should be explained clearly about the complications of bariatric surgeries. Patient should be advised to maintain healthy weight by regulating the regular calorie intake and performing regular exercise.

**Conclusion**
According to WHO, behavioural and environmental factors are responsible for rapid increase in obesity for last two decades. Non-pharmacological treatment includes dietary modifications and lifestyle modifications. Pharmacological treatment includes use of appetite suppressants and lipase inhibitors. Bariatric surgeries are also performed but are associated with complications.

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