Obesity: Pathophysiology, Health Implications, and Therapeutic Interventions

ABSTRACT

Obesity is a significant health issue defined by the excessive accumulation of fat that poses serious health risks. A Body Mass Index (BMI) exceeding 24 is categorised as overweight, while a BMI over 30 is considered obese. Obesity is a major contributor to various chronic diseases, including cardiovascular issues such as heart disease and stroke, which rank among the leading causes of death globally. Currently, more than 800 million people worldwide are living with obesity, and the medical expenses related to this condition are expected to surpass $1 trillion by 2025. Furthermore, individuals with obesity face twice the likelihood of hospitalization if they test positive for COVID-19.

The weight loss industry plays a significant role in the overall revenue of the dietary supplements market. Anti-obesity medications act as pharmacological agents aimed at reducing or managing body weight. These drugs can alter essential physiological processes involved in weight regulation by affecting either appetite or calorie absorption. Effective management of obesity is vital to reduce its health consequences and associated financial burdens.

Keywords: Obesity, BMI, Weight Loss, Pathologies, Anti-Obesity Drugs.

INTRODUCTION

“Obesity is a complicated condition marked by an excessive accumulation of body fat, which raises the risk of various health issues, including heart disease, diabetes, high blood pressure, and certain cancers. Several factors contribute to the difficulty some individuals face in avoiding obesity, typically resulting from a mix of genetic factors, environmental influences, and personal choices related to diet and exercise” [1].

A person is typically considered obese if they exceed their ideal weight by more than 20%, with this ideal weight depending on factors such as height, age, sex, and body composition.

“Obesity is characterized by an enlargement of adipose cells, which occurs due to the buildup of fat in the cytoplasm of adipocytes. This metabolic change is regulated by various enzymes, including fatty acid synthase, lipoprotein lipase, and adipocyte fatty acid-binding protein. Ultimately, obesity stems from an imbalance between energy intake and energy expenditure. Lipogenesis refers to the process of storing free fatty acids as triglycerides (TG). In contrast, lipolysis involves the breakdown of stored triglycerides into free fatty acids and glycerol. Obesity is frequently linked to hyperlipidemia, which is marked by elevated lipid levels in the blood” [2-3].

How to Assess Obesity

“Obesity is a medical condition defined by an excessive buildup of body fat that may adversely affect health. It is primarily assessed using Body Mass Index (BMI) and further evaluated

through fat distribution measurements, such as the waist-hip ratio, along with total cardiovascular risk factors. BMI is closely linked to both the percentage of body fat and total body fat. In children, healthy weight ranges differ based on age and sex" [4].

Table:1 Classification of BMI and Associated Risk of Co-Morbidities

Classification	**BMI (kg/m²)**	**Risk of Co-Morbidities**
Underweight	< 18.5	Low (but increased risk of other clinical problems)
Normal weight	18.5 – 24.9	Average
Overweigh t	25.0 – 29.9	Mildly increased
Obese	≥ 30	
Obese I	30.0 – 34.9	Moderate
Obese II	35.0 – 39.9	Severe
Obese III	≥ 40	Very severe

Body Mass Index (BMI):

BMI is a metric that relates an individual's weight to their height.

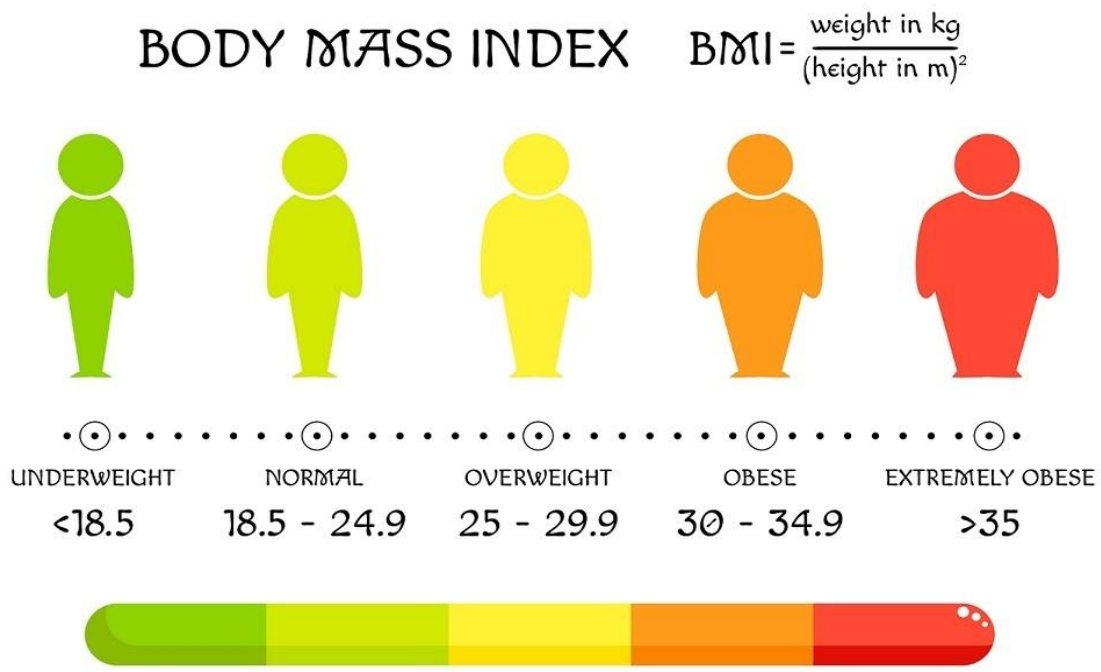

Fig.1. Body mass Index

Formula:

BMI = kg/m2

Waist to Hip Ratio (WHR):

WHR is a measurement used to evaluate body fat distribution, particularly in the abdominal area, which can indicate greater health risks [5].

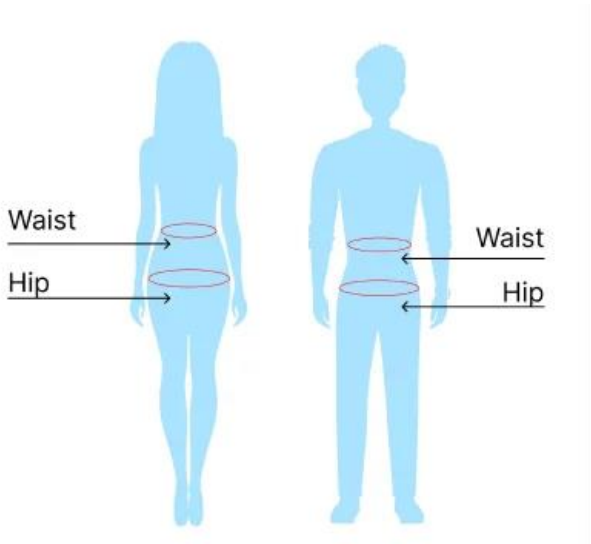

Fig.2. Waist to Hip Ratio

Formula:

$$\text{WHR} = \frac{\text{Waist Circumference}}{\text{Hip circumference}}$$

Risk Indicators:

Men: A WHR above 0.90 suggests increased health risks.

Women: A WHR above 0.85 suggests increased health risks.
Higher Risk: Women with a WHR greater than 0.8 and men with a WHR greater than 1.0 face a higher risk of health complications [6].

Health Implications: WHR is considered a more accurate predictor of cardiovascular disease compared to BMI and waist circumference, as it highlights the central distribution of body fat, which is associated with various health issues.

CAUSES OF OBESITY

Obesity develops when the body accumulates excessive fat, typically due to a sustained imbalance where energy intake surpasses energy expenditure. Various factors contribute to the growing prevalence of obesity.

A. Genetics

Genetics significantly influence obesity. Children of obese parents are more likely to become obese themselves, though this does not mean obesity is entirely predetermined. Lifestyle choices, particularly diet, can affect gene expression. Some individuals may have genetic traits that make weight loss more challenging [7-8].

Genetic causes of obesity can be classified into three categories:

1. Monogenic Obesity: Resulting from mutations in a single gene, often impacting the leptin-melanocortin pathway.

2. Syndromic Obesity: Severe obesity associated with other characteristics, such as neurodevelopmental issues and organ malformations.

3. Polygenic Obesity: Caused by the combined influence of multiple genes, especially in environments that encourage weight gain.

B. Diet Intake

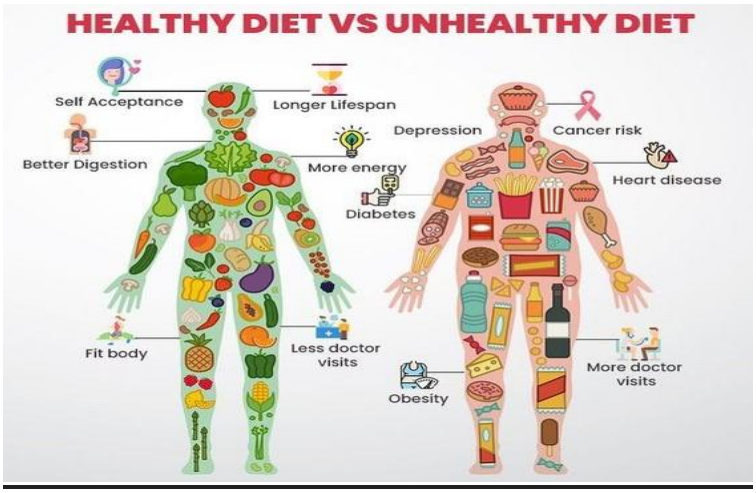

Fig.3. Healthy Vs Unhealthy diet

C. Unhealthy Diet: A diet that is high in calories but low in fruits and vegetables, along with excessive consumption of junk food and large portions, can lead to weight gain.

D. **Liquid Calories:** Many people can consume a substantial number of calories through beverages without feeling full, especially from alcohol and sugary drinks like sodas, which can contribute to increased body weight.

E. **Sedentary Lifestyle:** Living a sedentary lifestyle allows for the easy consumption of excess calories. Engaging in screen time on computers, tablets, and phones is a sedentary behavior, and the amount of time spent in front of screens is strongly associated with weight gain.

F. **Leptin Resistance:** Leptin is a hormone that plays a vital role in obesity. It is produced by fat cells, and its levels rise with increased fat mass, making leptin levels particularly high in individuals with obesity. In healthy individuals, elevated leptin is associated with reduced appetite, signaling the brain about fat reserves. However, many obese individuals experience leptin dysfunction, as it struggles to cross the blood-brain barrier. This condition, referred to as leptin resistance, is believed to be a major contributor to the onset of obesity.

G. **Health Conditions and Medications:** Certain medical conditions and hormonal imbalances can contribute to being overweight or obese. Conditions like an underactive thyroid, Cushing syndrome, and polycystic ovary syndrome (PCOS) can influence weight. Cushing syndrome involves high cortisol levels (the stress hormone), which can lead to weight gain. PCOS causes an imbalance in female reproductive hormones, making weight management more challenging. Additionally, some medications, including certain corticosteroids, antidepressants, and anti-seizure drugs, may also lead to weight gain.

H. **Stress, Emotional Factors, and Poor Sleep:** Emotional issues can cause some individuals to eat more than usual when feeling bored, angry, upset, or stressed. Studies have shown that inadequate sleep increases the risk of being overweight or obese, partly because hormones released during sleep regulate appetite and the body's energy expenditure [9-10].

PATHOLOGIES AND EFFECTS ON HEALTH ASSOCIATED WITH OBESITY

Obesity is linked to a greater incidence of various health conditions.

Diabetes Mellitus: Obesity is the leading cause of diabetes and impaired glucose tolerance. In individuals with obesity, adipose tissue releases significant amounts of non-esterified fatty acids, glycerol, pro-inflammatory cytokines, and hormones. These substances contribute to the development of insulin resistance, resulting in hyperinsulinemia, reduced insulin receptor sensitivity, and overstimulation of pancreatic cells. Both insulin resistance and hyperinsulinemia are viewed as outcomes of the interaction between increased body weight and genetic predispositions. Research shows that while insulin sensitivity may be comparable between non-diabetic offspring of parents with type 2 diabetes and those from non-diabetic

parents with nearly ideal body weight, insulin sensitivity tends to decline more rapidly with increasing body weight in individuals with a family history of diabetes.

Cardiovascular Disease: "Obesity is associated with an elevated risk of metabolic diseases and cardiovascular disease (CVD). The accumulation of excess body fat contributes indirectly to cardiovascular issues through thromboembolic diseases and several major risk factors, such as hyperlipidemia, type 2 diabetes, high blood pressure, and metabolic syndrome. Metabolic syndrome is defined by a combination of characteristics, including central obesity, high serum triglyceride levels, low serum high-density lipoprotein (HDL) cholesterol levels, hypertension, and elevated fasting blood glucose levels" [11].

Respiratory Disease: Obesity is associated with an increased risk of chronic respiratory conditions, such as asthma, obstructive sleep apnea, obesity hypoventilation syndrome (OHS), and pulmonary hypertension. These disorders can worsen complications like acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD). Obesity affects respiratory mechanisms by increasing airway resistance, altering breathing patterns, and disrupting gas exchange. These changes are thought to result from the added elastic load of excess weight on the thorax and abdomen, an increase in pulmonary blood volume, and mismatched ventilation and perfusion.

Cancer: Being overweight or obese raises the risk of developing certain cancers.
Increased Insulin and IGF-1 Levels: Higher levels of insulin and insulin-like growth factor-1 (IGF-1) can contribute to the development of various cancers.
Chronic Inflammation: Obesity is often accompanied by chronic, low-grade inflammation, which is linked to a greater risk of certain cancers.
Estrogen Production: Fat cells produce elevated amounts of estrogen, which may heighten the risk of cancers such as breast cancer. Additionally, fat cells can influence processes that regulate the growth of cancer cells.

Hepatocellular carcinoma is associated with fatty liver disease linked to obesity. As this condition progresses from steatosis to cirrhosis, it becomes a risk factor for hepatocellular cancer. In obese individuals, high levels of leptin may serve as a growth-promoting factor for this type of cancer.
"Pancreatic cancer is also associated with obesity due to inflammatory adipokines that disrupt glucose transport, leading to insulin resistance. This, along with hyperinsulinemia, hyperglycemia, and lipotoxicity, can result in inflammation and eventual exhaustion of pancreatic β-cells" [12].

Anti-Obesity Drugs for Long-Term Use: Anti-obesity medications typically work by suppressing appetite, inhibiting fat absorption, or increasing energy expenditure and thermogenesis.
Some of these drugs are specifically designed for weight loss.

1. Orlistat

“Orlistat is a selective inhibitor of pancreatic lipase, which helps reduce the intestinal digestion and absorption of fat. It is approved by both the FDA and the European Medicines Agency (EMA) and is available in a 120 mg prescription form (taken three times a day before meals) and a 60 mg over-the-counter version. People with obesity using orlistat can expect to lose an additional 2.9–3.4 kg over a 12-month period. Common side effects include gastrointestinal issues, decreased absorption of fat-soluble vitamins, and steatorrhea. The main mechanism of orlistat involves blocking gastric and pancreatic lipases, preventing the breakdown of triglycerides and the absorption of fatty acids in the intestines. This action inhibits the absorption of about one-third of dietary fat, thereby reducing calorie intake without affecting appetite. Additional metabolic benefits of orlistat include slight reductions in blood pressure (systolic: 1.15 mmHg; diastolic: 1.07 mmHg) and lower circulating lipid levels (total cholesterol: 0.30 mmol/l; low-density lipoprotein (LDL) cholesterol: 0.27 mmol/l; triglycerides: 0.09 mmol/l). Common side effects include fatty or oily stools, increased bowel movements, fecal urgency, gas, as well as gastrointestinal discomfort such as diarrhea, bloating, abdominal pain, and dyspepsia” [13].

2. Liraglutide

Liraglutide (Saxenda) is an injectable glucagon-like peptide-1 (GLP-1) derivative that received FDA approval in 2014 for weight management, with a recommended dose of 3.0 mg administered subcutaneously (SC) daily. A lower dose (Victoza) was approved in 2010 for the treatment of type 2 diabetes, with a recommended dose of 1.8 mg SC daily. Liraglutide aids weight loss by enhancing feelings of fullness through stimulation of the hypothalamus and delaying gastric emptying, which helps reduce food intake.

The mechanism of liraglutide involves the secretion of GLP-1 from the distal ileum and proximal colon after meals, as well as from the vagal nucleus of the solitary tract. As an incretin hormone, GLP-1 primarily regulates blood glucose by inhibiting glucagon secretion and promoting insulin release from pancreatic beta cells in a glucose-dependent manner. Furthermore, GLP-1 slows gastric emptying, increases post-meal satiety, and decreases appetite by acting on the hypothalamus and limbic/reward systems. Treatment with liraglutide can lead to reductions in waist circumference, lipid levels, HbA1c, blood pressure, blood sugar, and insulin levels, in proportion to the amount of weight lost.

THERAPEUTICS OF OBESITY:

Lifestyle modification:

In the absence of pharmacological interventions, “lifestyle changes” remain the mainstay of obesity management. It is recommended that obese individuals lose at least 10% of their body weight through diet, physical activity, and behavior (or lifestyle changes). You can achieve significant weight loss in a short period of time by controlling the foods you eat. Long-term

weight management can be achieved through increased physical activity and patient-physician communication. In many cases, lifestyle changes can significantly reduce the risk of cardiovascular disease.

Stay Active:
Aim to walk for at least 30 minutes each day, especially before breakfast, to help burn fat. Regular exercise is an effective way to reduce excess body fat and maintain muscle tone.

Ensure Regular Bowel Movements:
Add extra fiber to your daily diet to promote digestive health.

Limit Animal Fats:
Avoid foods like butter, cream, ice cream, whole milk, rich dressings, mayonnaise, and fried foods.

Focus on Fresh Produce:
Incorporate plenty of fresh fruits and vegetables into your meals, as they are excellent sources of fiber. Try to have at least one meal each day that consists entirely of fruits and vegetables.

Consult a Healthcare Provider:
If you suspect you have an underactive thyroid, speak with your doctor, as this condition can contribute to weight gain [14-15].

CONCLUSION

Obesity is a complex, chronic condition influenced by a range of factors, including dietary habits, lifestyle choices, genetics, and environmental influences. While lifestyle and behavioral changes are essential for successful weight loss, maintaining these healthy habits can be difficult. Some anti-obesity medications may help support individuals in reaching their weight-loss objectives. However, many of these drugs target only specific components of this multifaceted issue and may have side effects. Combining medications, such as phentermine with topiramate or naltrexone with bupropion, could potentially enhance their effectiveness, but their long-term safety and tolerability require careful assessment in the future. Ultimately, successful weight loss hinges on consistent adherence to a low-calorie diet and regular physical activity.

In conclusion, a better understanding of the various dimensions of obesity, including propensity to regain lost weight, interindividual differences in pathogenesis, and response to treatment, is needed to develop effective and cost-effective interventions. These findings will in turn benefit related health complications such as the incidence of diabetes. More research is needed to identify behavior modifications that are effective and accessible to people from different backgrounds. More studies have been conducted to develop more effective and safer medications to help obese people lose weight and maintain a healthy weight long-term. In addition, we need to devote more effort and resources to obesity prevention in both children and adults. Prevention is key because treatment alone is not very effective and cannot reverse the obesity epidemic in the long term.

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