Obesity, A Threat to Global Health: A Review

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ABSTRACT

Obesity is one of the most serious life threatening health problems of the 21st century which affects nearly 300 million people worldwide that in turn would trigger additional pathologies such as cardiorespiratory dysfunctions, cancer, gastrointestinal disturbances, and type2 diabetes mellitus. Obesity has a multifactorial nature resulting from genetic, physiological, behavioural, and environmental factors that lead to an imbalance between energy intake and expenditure. However, the key to success in tackling this problem lies in prevention and this in itself mandates a rigorous understanding of the physiology of weight control and the pathogenesis of obesity. Conventional therapies such as lifestyle modification (diet and exercise) recommended as the cornerstone of obesity management. The Food and Drug Administration (FDA) has approved five long-term obesity drugs for adults who are obese so far: orlistat, lorcaserin, liraglutide, phentermine/topiramate, and naltrexone/bupropion over the past two years. When treating an obese patient for any given disease, several physiological changes may impact the pharmacokinetic properties of the drugs required. Therefore, pharmacotherapy remains important but is limited by their results in terms of weight loss. Additionally, several medical devices are available for short-term and long-term use. Bariatric and metabolic surgical interventions (gastric banding, sleeve gastrectomy, and Roux-en Y gastric bypass) are endorsed by many international societies to be an effective treatment for weight loss, which also offers significant improvement in associated comorbidities and reduce mortality for patients with severe obesity.

Keywords: Bariatric surgery, Co-morbidities, Diet, Exercise, Obesity.

1) INTRODUCTION

Obesity may be a common and preventable disease of clinical and public health importance. [1, 2] It is often a major risk factor for the development of several non-communicable diseases, significant disability and premature death. [1] Obesity is defined as a condition of abnormal or excessive fat accumulation in adipose tissue. [1,3,2] In the young adult normal levels of body fat are considered to be 12–20 % body weight in males and 20–30 % bodyweight in females, while levels of > 25 % body weight in males and > 33 % body weight in females can be considered obese. [3] The amount of excess fat in absolute terms, and its distribution in the body - either around the waist and trunk (abdominal, central or android obesity) or peripherally around the body (gynoid obesity). [1] A growing number of people, including children, suffer from obesity, especially in the Western society. [4] A rapid increase in childhood obesity has also been reported. Obesity among Ghanaian adults is common, particularly among the elderly, females and urban dwellers. [5] Obese humans show elevated levels of leptin in serum and adipocytes. [4] Obesity is associated with a greater risk of disability or premature death due to type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) such as hypertension, stroke and coronary heart disease as well as gall bladder disease, certain cancers (endometrial, breast,
prostate, colon) and non-fatal conditions including gout, respiratory conditions, gastro-esophageal reflux disease, osteoarthritis and infertility. A central distribution of body fat is related to a better risk of morbidity and mortality than a more peripheral distribution. Sparingly, obesity may be a manifestation of other medical conditions such as hypothyroidism, Cushing’s syndrome and certain hypothalamic disorders. From a large body of evidence, the global epidemic of obesity has resulted mainly from societal factors that promote sedentary lifestyles and the consumption of high-fat, energy dense diets. [1]

2) EPIDEMIOLOGY

Obesity is a complex, multifactorial, and largely preventable disease affecting, along with overweight, over a third of the world’s population today. [5, 6] If secular drift continues, by 2030 an approximate 38% of the world’s adult population will be overweight and another 20% will be obese. Fueled by economic growth, industrialization, mechanized transport, urbanization, an increasingly sedentary lifestyle, and a nutritional transition to pre-packaged foods and high calorie diets over the last 30 years, many countries have witnessed the widespread presence of obesity in its citizens double, and even quadruple. [6] The WHO recommended cut-off point for obesity corresponds to a percentage body fat of 25 percent and 35 percent in men and women, respectively. [2] The worldwide prevalence of overweight and obesity has doubled since 1980 to an extent that nearly a third of the world population is now classified as overweight or obese. In low-income countries, obesity is generally more prevalent among middle-aged adults from wealthy and urban environments (especially women); whereas, in high-income countries, it affects both sexes and all ages, but its prevalence is disproportionately greater among disadvantaged groups. [5] The prevalence of overweight appears to increase with age. In 1999–2004, older adults were more likely to be obese than their younger counterparts. The only exception was adults aged 80 and older who were not significantly different from the 20- to 39-year-old adults. Among adults 20–39 years of age, 26.8% were obese. Among 40- to 59-year-old adults 34.8% were obese, and among 60- to 79-year-old adults 35.2% were obese, whereas among older adults (80 y) 17.3% were obese. Among children, the highest prevalence of overweight was among school-age children and adolescents; 11.5% of preschool-age children 2–5 years, 16.8% of school-age children 6–11 years, and 16.5% of adolescents 12–19 years were classified as overweight. [7] The increase in the prevalence of obesity in developing countries is mainly due to rapid changes in socioeconomic status and demographic, and the adoption of an energy- and fat-rich diet and a sedentary lifestyle. [5] The number of overweight and obese men and women has risen since 1960 in the last decade, the percentage of adults, ages 20 years or older, who are in these categories has increased to 54.9 percent. Overweight and obesity are especially evident in some minority groups, as well as in those with lower incomes and less education. [8]

3) ETIOLOGY

Obesity has emerged as one of the most serious public health concerns in the 21st century, and the morbidity and mortality associated with obesity continue to increase. Endogenous (that is, genetic) and exogenous factors (that is, diet and physical activity) have an important role in the assessment and management of obesity. [9]

- Genetic factors

Family and genetic factors play an important role in the development of obesity. Through the mechanism of thrifty genes, humans have evolved developing the ability to deposit fat and thus utilize it during periods of energy deficit. This ability for depositing fat has possibly turned into a detriment for developed societies in which
overabundance and easy access to foods are the norm. [10] A recent study identified a region on human chromosome 2 that accounted for 47% of the variation in serum leptin concentrations and 32% of the variation in fat mass in a population of Mexican-Americans. [11] Mutations in human genes coding for leptin (LEP), leptin receptor (LEPR), pro-opiomelanocortin (POMC), and melanocortin-4 receptor (MC4R) have been associated with juvenile-onset morbid obesity. [2]

- Environmental and lifestyle factors
  
  (a) Sedentary Habits: Obesity is more frequent in sedentary persons as compared to those that regularly practice Physical Activity. It’s been observed that individuals who dedicate more time to sedentary activities and don’t regularly do sports more frequently have problems with excess body weight.
  
  (b) Diet: Greater risk of obesity has been estimated for persons having low fruit and vegetable consumption and a high fat intake, especially in saturated fatty acids. In certain countries, habitual alcohol consumption has also been associated with excess weight.
  
  (c) Parity: Women who had given birth to a greater number of children were more frequently obese. [10]
  
  (d) Smoking: Increased BMI has also been associated with persons who quit smoking. [7,10]
  
  (e) Sleeping pattern: Short sleep duration may be accompanied by obesity from childhood to adulthood. [9,10]

4) CLINICAL MANIFESTATION

- Obesity adversely affects nearly all physiological functions of the body and comprises a significant public health threat. It increases the risk for developing multiple disease conditions, such as diabetes mellitus, cardiovascular disease, several types of cancers, an array of musculoskeletal disorders, and poor mental health, all of which have negative effects on the quality of life, work productivity, and healthcare costs. [5]
  
  • Obesity is a major contributor to the metabolic dysfunction involving lipid and glucose, but on a broader scale, it influences organ dysfunction involving cardiac, liver, pulmonary, endocrine, and reproductive functions. [12]
  
  • Obesity contributes to immune dysfunction from the effects of its secretion of inflammatory adipokines and is a major risk factor for many cancers. [12, 13]
  
  • Gastrointestinal Symptoms: Gastrointestinal (GI) symptoms are extremely common in the general population, yet remain poorly understood among obese individuals. Studies assessing GI symptoms have produced conflicting results with some studies suggesting that conditions such as Gastroesophageal Reflux Disease (GERD) is associated with an increased BMI.
  
  • Abdominal pain: There was an association between increased BMI and increased abdominal pain, with those overweight, those obese and those morbidly obese; however, these were not statistically significant. [14]
  
  • Obesity and overweight status are common comorbidities in Fibromyalgia Syndrome (FMS) patients. Obesity is associated with increased sensitivity to pain, poor health status, and a low health-related quality of life. [15]
  
  • In severe obesity, sleep apnoea may occur in up to 50% of patients. [16]
  
  • Childhood obesity
    
    Prenatal Influences: The infant of a diabetic mother is an imitation for the influences of fetal over nutrition on subsequent adiposity. Subjection of the fetus to high concentrations of ambient glucose stimulates fetal hyperinsulinism, increased lipogenesis, and macrosomia. Because gestational diabetics frequently are obese, it is difficult to separate the metabolic consequences of gestational obesity and diabetes on subsequent adiposity of the

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infant of a diabetic mother from the possibility that the mother has passed a genetic tendency toward obesity to her offspring.

Postnatal Influences: Television watching encourages inactivity and the consumption of calorically dense foods.\[^{11}\]

- Traumatic factors
  (a) Chemical induced obesity: Mercury was claimed to induce obesity as a frequent by-product of prolonged courses of treatment.
  (b) Endocrine factors are responsible for 5% of obesity cases, overeating for 95%.\[^{17}\]
  - According to the conventional underpinning, leptin resistance confers chronic overeating that impels storage of excess energy as fat depots which underlies the accelerated rate of weight gain.\[^{18}\]

5) NORMAL PHYSIOLOGY OF ENERGY BALANCE

Basic components of energy balance include energy intake, energy expenditure and energy storage.\[^{19}\]

a) AFFERENT (Role of leptin and ghrelin)

Two of the hormones that appear to play a crucial role in the regulation of food intake and weight are leptin and ghrelin. Both originate within the periphery and signal through different pathways to the brain, particularly to the hypothalamus.\[^{4}\]

The invention of leptin was a serious milestone in elucidation of the communication between the brain and energy stores.\[^{20}\] The human obese (OB) gene and its product leptin were identified in 1994. The OB gene is located on chromosome 7.\[^{4}\] Leptin is derived from Greek word leptin means thin. Leptin is an anorexigenic adipokine with 167 amino acids and is produced primarily by fat and it’s also produced by non-adipose tissue like stomach, placenta, striated muscle and mammary epithelium where, leptin mainly acts on thermogenesis and decrease food intake.\[^{21}\] The leptin acts both at short term and future on food intake and body weight.\[^{4,22}\] Leptin acts on leptin receptors (LepRs) which are abundantly found within the hypothalamus. Leptin easily crosses the blood–brain barrier through a saturable transport and acts on hypothalamic neurons; it inhibits expression of orexigenic Agouti Related Peptide (AgRP), Neuro-Peptide Y (NPY), and alpha-melanocyte-stimulating hormone (MSH) and stimulates anorexigenic, Pro-opiomelanocortin (POMC) and Cocaine and amphetamine (CART), inhibits NPY/AgRP neurons, leading to reduced food intake.\[^{4,20-23}\]

Ghrelin was identified originally as an endogenous ligand for the expansion hormone secretagogue receptor (GHS-R) in rat stomach.\[^{23}\] Ghrelin may be a 28–amino acid peptide synthesized mainly within the stomach.\[^{20}\] The gene coding for human prepro-ghrelin, GHRL, is located on chromosome 3. Human prepro-ghrelin consists of 117 amino acids. The secretion of ghrelin by the stomach depends largely on the nutritional state.\[^{4}\] Although the stomach is the main site of secretion, ghrelin is also secreted by the pituitary, hypothalamus, lungs, heart, and pancreas. Exogenous ghrelin is understood to stimulate food intake\[^{4,22}\] Ghrelin stimulates the activity of neurons expressing NPY, AgRP and orexin. On the opposite, ghrelin has an inhibitory effect on POMC neurons and CRH-producing neurons. Both ghrelin and leptin plays a crucial role within the system for energy balance in humans.\[^{4}\]

b) HYPOTHALAMUS (Feeding and satiety center, energy metabolism)

The hypothalamus primary function is to take care of the body’s energy established order.\[^{24}\] The hypothalamus controls weight and appetite.\[^{24,25}\] Under conditions of stable weight, there is a balance between food intake and metabolism.\[^{26}\] Hypothalamus, posses several neuronal centers like that in lateral hypothalamic nuclei considered to be “hunger” center and in ventromedial nuclei serving because the “satiety” center. There are two differing types of neurons in ARC that are important on top of things of food intake;
(1) Neurons operated by orexigenic peptides like ghrelin that release the substances involving neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP) in hunger center.

(2) Neurons operated by anorexigenic hormones and releasing alpha-melanocyte stimulating hormone

Appetite Regulating Hormones:
- NPY: Neuropeptide Y
- AgRP: Agouti related peptide
- MSH: alpha-melanocyte-stimulating hormone
- CART: Cocaine and amphetamine regulated transcript
- Oxerins
- Leptin
- Ghrelin
- Glucagon like peptide-1
- Oxynotomodulin
- PYY3-36. [21]

There’s growing evidence that carboxylic acid metabolism within a discrete hypothalamic region functions as a sensor of nutrient availability that integrates nutritional and hormonal signals to manage feeding behaviour, peripheral glucose metabolism and energy expenditure. [24]

Although autophagy is fundamentally considered a catabolic process, the studies overviewed here high light the importance of this pathway in sustaining and even enabling anabolic pathways in certain settings, autophagy-derived nutrients produced from the catabolic degradation of proteins, lipids, carbohydrates and ferritin all support diverse biosynthetic pathways. [27]

c) EFFERENT (Food intake and energy expenditure)

Energy balance refers to the physiological mechanisms that are reciprocally linked to make sure that adequate energy is out there for cellular processes required for survival and reproduction. [28] The primary law of thermodynamics is typically formulated as follows: the speed of change in body ES10 is adequate to the difference between the rates of E1 and EO. E1 primarily consists of the energy from the food and fluids we consume. EO includes the illuminated, conductive, and convective heat strayed; any work performed. The energy balance equation (ES=E1–EO). [29] Humans absorb energy within the sort of protein, carbohydrate, fat and alcohol. [19,29] fat, commonly called ‘fat’, provides the main storage of energy in mammals. [15] The skin may be a vital sensory organ for thermoregulatory control of energy expenditure. [30] Energy is consumed within the processes of physical activity, metabolism, and adaptive thermo genesis, all of which are modulated by the brain. [25] An individual who is extremely active might maintain energy balance and a healthy weight by eating and expending 3,000 kcal/day. That very same person, if adopting a sedentary lifestyle, could maintain energy balance and therefore the same healthy weight by eating and expending 2,000 kcal/day. High level of physical activity is related to low weight gain over time and relatively low levels of physical activity are related to high weight gain over time. A healthy weight is maintained with a high level of physical activity and a high energy intake and therefore the result’s weight gain and obesity which returns the system to a high energy throughput. [19]

6) PATHOGENESIS OF OBESITY

Obesity is a common but complex condition, which has a plurifactorial pathogenesis. [31,32] It includes complex combination of internal and external environmental factors such as imbalance between calorie intake and consumption of inappropriate diet especially fats and mono- saccharides, low physical activity and sedentary lifestyle which is a central perturbation that contributes weight gain. [32,33] Although environmental factors are important, there is considerable evidence that genes also have a significant role in its pathogenesis. [34] Obesity is a heritable trait influenced by the interplay of genetics has increased dramatically in the last decades. [32,35] Obesity can be either monogenic or
polygenic in inheritance. Six single gene defects have been identified:
a) Agouti related peptide (AgRP) or Neuropeptide Y (NPY) gene: Agouti related peptide promotes food intake through the activation of Y1 Sub-type or NPY Receptor. Over expression of AgRP or NPY gene causes weight gain which leads to obesity. 

b) Leptin gene: Leptin is produced in fat cells, the gut, and the placenta and signals the brain about the amount of stored fat. Deficiency causes hyperphagia, insulin resistance and infertility. In humans, leptin may act on the arcuate nucleus to decrease NPY production (which usually stimulates food intake). Obesity due to leptin deficiency has been reported in two families, affected subjects responding well to leptin therapy. In contrast the majority of obese subjects have a high level of circulating leptin level suggesting a level of leptin resistance.

c) Leptin receptor gene: Leptin receptor deficiency secondary to mutations in the leptin receptor gene has been reported in humans resulting in intense hyperphagia.

d) Pro-opio melanocortin (POMC): Deficiency in the POMC protein results in the absence of cleavage products of ACTH, α-MSH and β-endorphins. Due to the dual role of α-MSH in appetite regulation and pigmentation, the classic presentation is that of red hair and severe obesity. Adrenal insufficiency results from deficiency of ACTH.

e) Pro-convertase (PC1/2) deficiency: Pro-convertase-1/2 are neuroendocrine convertase endo-proteases that process large precursor proteins into mature bioactive products. Absence of activity of PC1/PC2 results in adrenal, gonadotropic, somatotropic, and thyrotropic insufficiency, along with postprandial hypoglycaemic

(Figure 1). A Schematic representation of peripheral signals and central pathways that regulates energy balance. When energy stores are low in adipose tissue, Ghrelin is released from the stomach and activates the appetite stimulating neurons. This in turn, will impact on energy balance by promoting food intake and inhibits energy expenditure. Conversely, when sufficient energy is stored in adipose tissue and individual is well fed, Leptin is released from adipose tissue and activates appetite suppressing neurons and inhibits appetite stimulating neurons which inhibits food intake and promotes energy expenditure. Obesity is a complex, heritable trait influenced by the interplay of six major Gene mutations such as AgRP*, Leptin gene*, Leptin receptor*, POMC*, PC1* and α MSH receptor*. Thus, causing imbalance between calorie intake and consumption of inappropriate diet especially fats and mono-saccharides, low physical activity and sedentary lifestyle which is a central perturbation that contributes weight gain. Asterisks (*) indicates mutations that have resulted in Human Obesity.
malaise caused by lack of insulin processing, in addition to severe early onset obesity. [31,35,38,39]

f) Melanocortin receptor (MC4R): The melanocortin receptor (MC4R) is a G-protein coupled, seven Trans membrane receptor, which is highly expressed in the hypothalamus, the region of the brain involved in appetite regulation. Studies indicate that the binding of MC4R with α-MSH, its high affinity ligand produced from POMC, inhibits feeding. Subsequently, mutations in MC4R, both in dominant and recessive form, have been demonstrated as the most common cause of inherited early-onset obesity with prevalence between 0.5–6% in different populations, affected individual demonstrate hyperphagia with food-seeking behaviour. [31,35,36,39]

6) COMPLICATIONS OF OBESITY

Obesity is considered as an epidemic in several countries and global obesity rates have increased exponentially in recent decades. [40,41] Although obesity has been labelled as a disease for over 200 years, only recently it has been recognized as a condition that in turn would trigger additional pathologies that warrants medical attention. [41,42] People are becoming obese younger, morbid obesity is increasing and severity of obesity in children and adolescents has provided greater emphasis on the wide variety of comorbid conditions and complications such as cardiovascular diseases, respiratory disorders, gastrointestinal disorders, musculoskeletal, metabolic disorders and others. [32,40,43,44]

The multiple medical complications of obesity are:

a) Cardiovascular diseases

Obesity puts stress on the cardiovascular system by increasing blood volume, stroke volume, cardiac output, total body oxygen consumption and systolic and diastolic blood pressure. Subsequent data analyses proved that the heightened frequency of cardiovascular stress in obese individuals could be largely accounted by the associated risk factors such as hypertension, atherosclerosis, congestive heart failure, venous stasis, deep vein thrombosis, cerebrovascular disease and stroke. [12,32,45,46]

b) Respiratory disorders

Comorbidities involving the respiratory system include obstructive sleep apnoea, which results from pharyngeal and sub mental fat accumulation within the confines of the upper respiratory tract, and hypo pharynx, which adversely affects ventilation, with secondary hypoxia and even hypercapnia. Excessive bronchial and peribronchial adipose cells secrete inflammatory adipokines that enhance bronchial mucosal and submucosal inflammation, causing reactive airway disease including asthma. [12,32,40,43,47]

c) Gastrointestinal disorders

Obesity is associated with increased prevalence of gall stones and gall bladder disease. In obesity, total body cholesterol production and biliary cholesterol output are increased beyond the solubilizing capacity of bile acids, so that the fluid becomes supersaturated with cholesterol, and cholesterol crystallization and stone formation are favoured. [12,43,45] It is also associated with greater risks of hernia, hepatic steatosis and severe pancreatitis. [32,40,43,46]

d) Renal disease

Overweight and obesity are relative risk factors for End-Stage Renal Failure (ESRF), kidney stones, glomerulopathy, chronic renal failure, calcific necrosis or calciphylaxis and urinary incontinence in women. [12,40,47]

e) Musculoskeletal disorders

Obesity is associated with significant reductions in physical activity levels and is one of the main risk factors for osteoarthritis due to increased adiposity and the injurious effects of inflammatory adipokines leading to enhanced degenerative joint disease. [12,40]

f) Metabolic changes

Obesity is an exaggeration of normal adiposity and is a major contributor in the pathophysiology of diabetes mellitus, insulin resistance, dyslipidaemia, largely
due to its secretion of excessive adipokines. Obesity is associated with a wide array of metabolic changes, most recently has been defined as the constellation of decreased insulin sensitivity causing type 2 diabetes mellitus. Dyslipidaemia may occur in children and adolescents as a result of obesity which includes high low density lipoprotein cholesterol, very low-density lipoprotein cholesterol, triglycerides and low levels of the protective high density lipoprotein cholesterol.

**g) Reproductive disorders**

In men, obesity is associated with reduced sperm count and increased rates of erectile dysfunction. In women, it also leads to menstrual irregularities or cessation of menstruation (Amenorrhea) decreased fertility, pregnancy complications and polycystic ovarian syndrome.**h) Cancer**

It is estimated that obesity accounts for quarter to one third of the colon, breast, endometrium, kidney and oesophagus cancer. It is also associated with increased risk of gastric, pancreatic and gallbladder cancer, as well as leukaemia.

(Figure 2). Medical complications of Obesity.

8) **DIAGNOSIS**

Obesity and overweight substantially increases the severity of health consequences and risk of mortality. The most commonly used criteria to assess the presence and the severity of obesity are body mass index, anthropometric measures such as skinfold thickness, waist circumference and waist-to-hip ratio. a) Body mass index: BMI describes relative weight for height, is significantly correlated with total body fat content. The advantages of BMI are that it is simple and most widely used to
assess overweight and obesity and to monitor changes in body weight.

BMI is calculated as weight (kg)/height squared (m^2). To estimate BMI using pounds and inches, use: \[\text{BMI} = \frac{\text{weight (pounds)}}{\text{height (inches)}^2} \times 703.\] \[44,49,51-54\]

### Table 1. World Health Organization Adult Body Mass Index Classification. \[50\]

<table>
<thead>
<tr>
<th>Classification of Overweight and Obesity</th>
<th>BMI (kg/m^2)</th>
</tr>
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<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
</tr>
<tr>
<td>Obesity class 1</td>
<td>30.0-34.9</td>
</tr>
<tr>
<td>Obesity class 2</td>
<td>35.0-39.9</td>
</tr>
<tr>
<td>Obesity class 3</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

b) Anthropometric measures

BMI is not always a reliable forecaster of body fat or fat distribution, particularly in muscular individuals because of the existent differences of fat and muscle proportion and distribution.\[32\] Other instruments to describe obesity, fat distribution, cardiovascular risk and mortality are:

- Waist circumference (WC): The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of risk factors and morbidity. Waist circumference is positively correlated with abdominal fat content and provides a clinically acceptable measurement for assessing a patient's abdominal fat content before and during weight loss treatment. \[48,49\]

  - The American Heart Association recommended 102 cm (40 in.) for men and 88 cm (35 in.) for women as cut-off levels for WC. \[32\]

- Waist to height ratio (WHtR): considered as, the best prospective indicator of cardiovascular risk as demonstrated several cross-sectional studies. \[32\]

c) Indirect measures of fat mass using underwater weighing, bioelectrical impedance is simple and non-invasive which estimates fat-free mass and total body fat. Dual energy X-ray absorptometry scanning, the gold standard for assessing total body fat and regional fat distribution. Both computerized tomography and magnetic resonance imaging are standard cumbersome and expensive procedures to estimate the visceral and subcutaneous fat area at L4-L5, and intrahepatic fat at T12-L1. \[48,55\]

### 9) TREATMENT

Obesity continues to be among the top health concerns across the globe and a modern approach to obesity acknowledges the multifactorial determinants of weight gain and the health benefits to be derived from weight loss. \[56,57\]

a) Non-pharmacological interventions for obesity.

Foundational to any weight loss effort have been focused on lifestyle significant modifications, diet and increased physical activity. \[41,56\]

- Diet: Obesity should be treated ideally with diets enriched with vegetables and fruit consumption followed, although with a lower grade of evidence, by whole grain cereals, low fat dairy products, fish, pulses, nuts, decreased meat intake, including processed meat and sugary foods. \[41,44,55,58\]

- Physical activities: The approach to which patients should to an exercise prescription describing frequency, intensity, type, and time with a minimum of 150 min moderate weekly activity.

Physical activity can be divided into two types: programmed and lifestyle. Programmed activity is typically planned, aerobic, and completed in a single bout (e.g., walking, biking, and aerobics classes). Lifestyle activity involves increasing energy expenditure throughout the day by methods such as using stairs rather than escalators or choosing a distant parking spot. An increase in physical activity is an important component of weight loss therapy since it leads to increased expenditure of energy and may also inhibit food intake in overweight patients. In addition, sustained physical activity can also be helpful in maintaining a desirable weight and reduces the overall CHD risk beyond that produced by weight reduction alone. \[41,56,59\]
b) Pharmacological interventions for obesity.

There are many angles to consider in drug treatment for obese patients who struggle with weight loss, management of medications and medical attention for prophylaxis, safe and efficacious treatment strategies are appropriate.[32,56,60] When treating an obese patient for any given disease, several physiological changes may influence the pharmacokinetic properties of the drugs required.[60]

Pharmacotherapy may be considered for individuals with a BMI >>30 kg/m² and for patients with a BMI >>27 kg/m² with the presence of an additional comorbid condition or more than one risk factor for ‘weight-related’ disease such as hypercholesterolemia, diabetes, hypertension.[41,49,59]

Pharmacological goal for obesity treatment consist of multiple targets and include:
• Inhibition of appetite (sibutramine)
• Inhibition of fat absorption (orlistat)
• Weight-regulatory brain circuits (cannabinoid receptor-1 (CB1) antagonists)
• Metabolism stimulation (CB1 antagonists; drugs that stimulate uncoupling proteins).[32]

Table 2. Drug Therapy for Weight Loss.[56]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dose / frequency</th>
</tr>
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<tbody>
<tr>
<td>Orlistat</td>
<td>Pancreatic lipase inhibitor</td>
<td>120 mg orally three times a day before meals</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>5-HT2C serotonin agonist with little affinity for other serotonergic receptors</td>
<td>10 mg orally twice a day</td>
</tr>
<tr>
<td>Phentermine/ topiramate</td>
<td>Sympathomimetic anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)</td>
<td>7.5 mg/46 mg or 15 mg/92 mg Orally indicated as rescue (requires titration)</td>
</tr>
<tr>
<td>Naltrexone/ bupropion</td>
<td>Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor</td>
<td>32 mg/360 mg orally (requires titration)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1 receptor agonist</td>
<td>3.0 mg Injection (requires titration)</td>
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c) Surgical intervention.

Surgery is one option for weight reduction for some patients with severe and resistant obesity, in whom efforts at other therapy have failed, and who are suffering from the complications of obesity. The aim of surgery is to modify the gastrointestinal tract to reduce net food intake and to achieve a weight loss that improves comorbid conditions and quality of life. [49,55]

• Bariatric surgery: The management of obesity and its associated complications has evolved in recent years, with a shift towards more definitive strategies such as bariatric surgery which is now considered as the most efficacious treatment for reducing excess body weight.[32,50] Bariatric surgery, the most intensive treatment for obesity, is appropriate only for those individuals with a BMI ≥40 kg/m² or BMI ≥35 kg/m² in the presence of comorbidities.[55,59] The gastrointestinal tract is transformed by surgery until decreases intraluminal capacity for food which can be achieved using the gastric banding technique (using an implanted medical device), the sleeve gastrectomy or biliopancreatic diversion with duodenal switch (including removal of a portion of the stomach) or using gastric bypass surgery, which reduce the stomach size in order to limit the gastric volume, and promote early satiety and thus reduce the oral intake. These techniques have an impact on the absorption of nutrients, therefore patients are advised to take lifelong nutrient supplements.[32,50,55,57,59]
10) CONCLUSION

Obesity is a complex chronic disorder that has significant implications for affected subjects. Obesity, besides impairing quality of life, is associated with numerous chronic diseases. In addition to the consequences, as obvious as the development of biochemical and physiological disorders of the body and shortening the life expectancy, it is also an economic and social problem, which has to be managed not only by well developed countries, but also those developing and with low income. Obesity, although it has reached the scale of the world epidemic, is no longer just a health issue and global obesity prevalence has not decreased. The scientific goal is to annotate obesity pathogenesis so as to better inform treatment, public policy, advocacy, and awareness of obesity in ways that ultimately diminish its public health and economic consequences. Diet and exercise are best for both prevention and treatment; but many patients do not achieve long-lasting benefits due to difficulty with adherence as well as physiological and neurohormonal adaptation of the body in response to weight loss. More therapeutic options are available today which offer a possible adjunct, but their effect is modest, they are limited by side effects, and the weight loss lasts only as long as the drug is being taken, immediately as treatment is stopped, the weight is regained. Further research into the physiology and pathophysiology of obesity, learning more about the combination of existing medications and new drug development should hopefully enable the development of preventive and therapeutic strategies to curb the obesity epidemic.

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