**Dr. Hayder .M Al-kuraishy Lec.8**

**Obesity** is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health. Obesity is most commonly caused by a combination of excessive food intake, lack of physical activity, and genetic susceptibility. Obesity is mostly preventable through a combination of social changes and personal choices.Changes to diet and exercising are the main treatments. Body mass index (BMI) is defined as the subject's weight divided by the square of their height and is calculated as follows.

BMI=body weight (kg)/m2

* **Any BMI ≥ 35 or 40 kg/m2 is severe obesity.**
* **A BMI of ≥ 35 kg/m2 and experiencing obesity-related health conditions or ≥40–44.9 kg/m2 is morbid obesity.**
* **A BMI of ≥ 45 or 50 kg/m2 is super obesity.**

Excessive body weight is associated with various diseases, particularly cardiovascular diseases, diabetes mellitus type 2, obstructive sleep apnea, certain type of cancer, osteoarthritis [[](https://en.wikipedia.org/wiki/Obesity#cite_note-HaslamJames-3) and asthma. As a result, obesity has been found to reduce life expectancy.

Obesity paradox: health outcomes in certain subgroups seem to be improved at an increased BMI, a phenomenon known as the obesity survival paradox.

In people with heart failure, those with a BMI between 30.0 and 34.9 had lower mortality than those with a normal weight. This has been attributed to the fact that people often lose weight as they become progressively more ill. Similar findings have been made in other types of heart disease. People with class I obesity and heart disease do not have greater rates of further heart problems than people of normal weight who also have heart disease.

Gut flora has been shown to differ between lean and obese humans. There is an indication that gut flora in obese and lean individuals can affect the metabolic potential. This apparent alteration of the metabolic potential is believed to confer a greater capacity to harvest energy contributing to obesity. Whether these differences are the direct cause or the result of obesity has yet to be determined unequivocally.

**Adipocytokines**

**Leptin** the "satiety hormone",is a hormone made by [adipose cells](https://en.wikipedia.org/wiki/Adipose_cells) that helps to regulate energy balance by inhibiting hunger. Leptin is opposed by the actions of the hormone [ghrelin](https://en.wikipedia.org/wiki/Ghrelin), the "hunger hormone". Both hormones act on receptors in the [arcuate nucleus](https://en.wikipedia.org/wiki/Arcuate_nucleus) of the [hypothalamus](https://en.wikipedia.org/wiki/Hypothalamus) to regulate appetite to achieve [energy homeostasis](https://en.wikipedia.org/wiki/Energy_homeostasis). In obesity, a decreased sensitivity to leptin occurs, resulting in an inability to detect satiety despite high energy stores. Leptin is produced primarily in the adipocytes of [white adipose tissue](https://en.wikipedia.org/wiki/White_adipose_tissue). It also is produced by brown adipose tissue, [placenta](https://en.wikipedia.org/wiki/Placenta) , ovaries, skeletal muscle, [stomach](https://en.wikipedia.org/wiki/Stomach) (the lower part of the [fundic glands](https://en.wikipedia.org/wiki/Fundic_glands)), [mammary](https://en.wikipedia.org/wiki/Mammary_gland) [epithelial cells](https://en.wikipedia.org/wiki/Epithelial_cell), bone marrow, gastric chief cells . Leptin levels in blood are higher between midnight and early morning, perhaps suppressing appetite during the night. The diurnal rhythm of blood leptin levels may be modified by meal-timing. Leptin acts on receptors in the lateral hypothalamus to inhibit hunger and the medial hypothalamus to stimulate satiety. In the lateral hypothalamus, leptin inhibits hunger by counteracting the effects of neuropeptide Y; a potent hunger promoter secreted by cells in the gut and in the hypothalamus, counteracting the effects of anandamide, another potent hunger promoter but in the medial hypothalamus, leptin stimulates satiety . The absence of leptin (or its receptor) leads to uncontrolled hunger and resulting obesity. Melatonin also appears to increase leptin levels in the presence of insulin, therefore causing a decrease in appetite during sleeping. Partial sleep deprivation has also been associated with decreased leptin levels. Although leptin reduces appetite as a circulating signal, obese individuals generally exhibit a higher circulating concentration of leptin than normal weight individuals due to their higher percentage body fat. These people show resistance to leptin, similar to resistance of insulin in type 2 diabetes, with the elevated levels failing to control hunger and modulate their weight.

**Adiponectin** is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid oxidation. Adiponectin is exclusively secreted from adipose tissue into the bloodstream and is very abundant in plasma relative to many hormones. adiponectin inversely correlated with body mass index in patient . However, a meta analysis was not able to confirm this association in healthy adults. higher in females than males, and are reduced in diabetics compared to non-diabetics. Weight reduction significantly increases circulating concentrations.

**Resistin** it was called "resistin" because of it involved in the induction of insulin resistance. Serum resistin levels increase with obesity .Resistin has been shown to cause "high levels of 'bad' cholesterol (low-density lipoprotein or LDL), increasing the risk of heart disease resistin increases the production of LDL in human liver cells and also degrades LDL receptors in the liver. As a result, the liver is less able to clear 'bad' cholesterol from the body. Resistin accelerates the accumulation of LDL in arteries, increasing the risk of heart disease.

 **Ghrelin** ("hunger hormone", is a peptide hormone produced by ghrelinergic cells in the gastrointestinal tract which functions as a neuropeptide in the central nervous system. Besides regulating appetite, ghrelin also plays a significant role in regulating the distribution and rate of use of energy. When the stomach is empty, ghrelin is secreted. When the stomach is stretched, secretion stops.  It acts on hypothalamic brain cells both to increase hunger, and to increase gastric acid secretion and gastrointestinal motility to prepare the body for food intake.  Ghrelin also plays an important role in regulating *reward perception* in dopamine neurons that link the ventral tegmental area to the nucleus accumbens (a site that plays a role in processing sexual desire, reward, and reinforcement, and in developing addictions) through its [colocalized](https://en.wiktionary.org/wiki/colocalize) receptors and interaction with dopamine and acetylcholine.



**Pharmacology of obesity**

Orlistat a potent natural inhibitor of lipases isolated from the bacterium *Streptomyces toxytricini*.  Orlistat also modestly reduces blood pressure and appears to prevent the onset of type 2 diabetes, whether from the weight loss itself or to other effects. Orlistat works by inhibiting gastric and pancreatic lipases, the enzymes that break down triglycerides in the intestine. When lipase activity is blocked, triglycerides from the diet are not hydrolyzed into absorbable free fatty acids, and instead are excreted unchanged. Only trace amounts of orlistat are absorbed systemically; the primary effect is local lipase inhibition within the GI tractafter an oral dose. The primary route of elimination is through the feces. Orlistat was also recently found to inhibit the thioesterase domain of fatty acid synthase (FAS), an enzyme involved in the proliferation of cancer cells but not normal cells.

 **Side effects**

Steatorrhea (oily, loose stools).

**Indications**

* Obesity
* Prevention of type 2 diabetes in an obese population
* Reduction in blood pressure

**Contraindicated**

* Malabsorption
* Hypersensitivity to orlistat
* Reduced gallbladder function (e.g. after cholecystectomy)
* Pregnancy and breastfeeding
* Use caution with: obstructed bile duct, impaired liver function, and pancreatic disease

**Lorcaserin** is a selective 5-HT2C receptor agonist, 5-HT2C receptors are located almost exclusively in the brain, and can be found in the choroid plexus, cortex, hippocampus, cerebellum, amygdale, thalamus, and hypothalamus. The activation of 5-HT2C receptors in the hypothalamus is supposed to activate proopiomelanocortin (POMC) production and consequently promote weight loss through satiety.

**Side effects**

  Headache, upper respiratory tract infection, nasopharyngitis , sinusitis  and nausea . Adverse events of depression, anxiety, suicidal ideation, cardiac valvulopathy

**Phentermine** is a psychostimulant drug similar to amphetamine. It is used medically as an appetite suppressant for short term use, as an adjunct to exercise and reducing calorie intake. phentermine primarily acts as a releasing agent of norepinephrine in neurons, although, to a lesser extent, it releases dopamine and serotonin into synapses as well. Phentermine may also trigger the release of monoamines, The primary mechanism of phentermine's action in treating obesity is the reduction of hunger perception, which is a cognitive process mediated primarily through several nuclei within the hypothalamus (in particular, the lateral hypothalamic nucleus, arcuate nucleus, and ventromedial nucleus). Outside the brain, phentermine releases norepinephrine and epinephrine – also known as noradrenaline and adrenaline respectively – causing fat cells to break down stored fat as well.

**Adverse effects include:**

* Cardiovascular effects like palpitations, tachycardia, high blood pressure, precordial pain; rare cases of stroke, angina, myocardial infarction, cardiac failure and cardiac arrest have been reported.
* Central Nervous System effects like overstimulation, restlessness, nervousness, insomnia, tremor, dizziness and headache; there are rare reports of euphoria followed by fatigue and depression, and more rare yet, psychotic episodes and hallucinations.
* Gastrointestinal effects include nausea, vomiting, dry mouth, cramps, unpleasant taste, diarrhea, and constipation.

**Sibutramine** is an oral anorexiant that is centrally-acting serotonin-norepinephrine reuptake inhibitor (SNRI) structurally related to amphetamines although its mechanism of action is distinct. Sibutramine is a monoamine reuptake inhibitor (MRI) that, in humans, reduces the reuptake of norepinephrine (by 73%), serotonin (by 54%), and dopamine (by 16%), thereby increasing the levels of these substances in synaptic clefts and helping enhance [satiety](https://en.wiktionary.org/wiki/satiety); the serotonergic action, in particular, is thought to influence appetite. Older anorectic agents such as amphetamine and fenfluramine force the release of these neurotransmitters rather than affecting their reuptake.Sibutramine is well absorbed from the GI tract (77%), but undergoes considerable first-pass metabolism, reducing its bioavailability. The drug itself reaches its peak plasma level after 1 hour and has also a half-life of 1 hour. Sibutramine is metabolized by cytochrome P450 isozyme CYP3A4 into two pharmacologically-active primary and secondary amines (called active metabolites 1 and 2) with half-lives of 14 and 16 hours, respectively. Peak plasma concentrations of active metabolites 1 and 2 are reached after three to four hours. The following metabolic pathway mainly results in two inactive conjugated and hydroxylated metabolites (called metabolites 5 and 6). Metabolites 5 and 6 are mainly excreted in the urine.

## Side effects

Cardiovascular events, heart attacks and strokes in patients with a history of cardiovascular disease.

increase blood pressure and heart rate in some patients.

cardiac arrhythmias, paresthesia, mental/mood changes (e.g., excitement, restlessness, confusion, depression, rare thoughts of suicide).

Symptoms that require urgent medical attention are seizures, problems urinating, abnormal bruising or bleeding, melena, hematemesis, jaundice, fever and rigors, chest pain, hemiplegia, abnormal vision, dyspnea and edema.

**Topiramate** is an anticonvulsant has been used as a treatment for alcoholism, obesity and antipsychotic-induced weight gain. The specific mechanism is unclear; however, it does mediate appetite suppression, satiety, and leads to a reduction in addictive food craving by antagonizing excitatory voltage-gated sodium also it increased energy expenditure by augmenting the activity of the inhibitory neurotransmitter γ-aminobutyric acid. Furthermore, topiramate appears to attenuate the adverse metabolic sequelae associated with obesity, independent of its weight loss properties, by enhancing insulin action, glucose transport, and adiponectin in adipocytes, skeletal muscle, and pancreatic beta cells.

**OTHER ANTI-OBESITY DRUGS**

**Metformin**

It is the only anti-diabetic drug that has been shown, in long term clinical trials, to reduce mortality and to prevent the development of diabetes. In some studies, weight reduction has been observed among non-diabetic individuals. Metformin is not currently licensed for the treatment of obesity, but it is a first line treatment in patients with type 2 diabetes, especially if they are obese.

**Liraglutide, like exenatide**, is a glucagon-like peptide-1 (GLP-1) analogue that was first used for the treatment of type 2 diabetes mellitus. As GLP-1 suppresses appetite and delays gastric emptying, liraglutide reduces body weight, even in non-diabetic individuals

**Myostatin** : increased peripheral tissue fatty acid oxidation through enhanced PPAR signaling are the two main mechanisms through which mice are protected against HFD-induced obesity in response to lack of or inhibition of myostatin. These findings highlight myostatin antagonists as a novel class of potential antiobesity drugs, which function by increasing energy expenditure, rather than limiting food/fat intake.

**Lorcaserin**: is a novel and selective 5-HT2C full agonist Lorcaserin differs from the earlier nonselective serotonin agonist's fenfluramine and dexfenfluramine, in that it exerts minimal activity on 5-HT2A and 5-HT2B receptors, which mediate the pathogenesis of serotonergic valvulopathy.18 Lorcaserin is indicated to promote weight loss in an obese population.

**Prieurianin:** prieurianin suppresses appetite and causes weight loss in diet-induced obese mice and inhibits adipogenesis in cell culture model of preadipocytes.

**Anti-obesity vaccination**

### Adipose tissue antigens

Oral immunization against pooled antigens derived from adipose tissue was used to modulate the inflammatory response. This therapeutical strategy demonstrated be safe and able to cause a significant reduction in waist and tight circumferences as well as improvement of lipid profiles, with a decrease in triglycerides and increase in HDL-cholesterol levels, despite having only a negligible effect on body weight.

### Somatostatin

The obese state is also characterized by a decreased growth hormone (GH) basal secretion and GH administration has been shown to reduce adiposity and increase lean mass. Somatostatin is a peptide hormone produced in the hypothalamus as well as in other tissues such as the gastro-intestinal system, which inhibits GH , anti-somatostatin vaccination decrease body weight gain .

### Glucose-dependent insulinotropic polypeptide

Glucose-dependent insulinotropic polypeptide formerly known as gastric inhibitory peptide (GIP) is a gastro-intestinal hormone secreted by the intestinal K-cells in response to the ingestion of carbohydrate and fat that stimulates glucose-dependent insulin release and secretion. Besides the pancreas, the GIP receptor (GIP-R) is widely distributed in peripheral organs including the adipose tissue where it holds a key role in fat deposition and lipid metabolism. Anti-GIP vaccine decreased fat accumulation and increased energy expenditure.

### Ghrelin receptor antagonists

Ghrelin receptor antagonists have demonstrated to decrease food intake, body weight and improve glucose tolerance due to increased glucose-dependent insulin secretion. Anti-ghrelin blocks ghrelin effects

**لشدّة رغبته بها ، قرّر قتلها كي يستعيد نفسه ، وإذ به يموت معها... فسيفُ العشق كسيف الساموراي ، من قوانينه اقتسام الضربة القاتلة بين السيّاف والقتيل**