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EMERGING DRUG FORMULATION AND DELIVERY SYSTEM FOR OBESITY MANAGEMENT

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Abstract

Obesity has become a major global health concern, contributing significantly to metabolic disorders, cardiovascular diseases, and diminished quality of life. Conventional therapeutic strategies, including lifestyle modification and pharmacotherapy, often demonstrate limited efficacy and are associated with systemic side effects. Recent advancements in pharmaceutical technology have enabled the development of innovative drug formulations and targeted delivery systems designed to enhance therapeutic efficacy while minimizing adverse effects. These emerging approaches include nanoparticle-based carriers, liposomes, polymeric micelles, and controlled-release formulations that improve bioavailability, enable site-specific targeting, and provide sustained drug release. Furthermore, combination therapies integrating anti-obesity agents with natural bioactive compounds are being explored for their synergistic potential. This review highlights recent trends in advanced drug formulation and delivery systems for obesity management, discussing their mechanisms, advantages, and clinical applications. Collectively, these novel strategies hold great promise for achieving safer, more effective, and personalized treatment outcomes in obesity management.

Keywords: Obesity management, drug delivery systems, nanocarriers, liposomes, polymeric micelles, controlled-release formulations, targeted therapy, anti-obesity agents, emerging therapeutics, and personalized medicine.

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Introduction

Worldwide, obesity is a multifaceted problem that has a significant impact on public health. It has the implicit to impact individualities across all periods and socioeconomic strata and poses pitfalls to all nations [1]. The accumulation of an excessive amount of fat in an individual's body with BMIs of 30 and 25-29.9, respectively, are referred to as obesity and overweight [2]. Because they can assist individuals in achieving and maintaining healthy weights, non-therapeutic treatments

are essential to the management of obesity. Behavioral and lifestyle changes, such as dietary changes, behavioral therapy, and increased physical activity, are non-pharmacological treatments for obesity. Physical activity helps burn calories, build muscle, and improve health in general. Overeating and a sedentary lifestyle [3], for example, are examples of unhealthy behaviors that contribute to weight gain that can be identified and changed through behavioral therapy.

In order to address critical issues in medication delivery, the design of MN arrays including their form, size, geometry, manufacturing materials, and procedures is crucial. The kind of active substance that is provided has an effect on the efficacy of MNA-based drug delivery. There are a variety of approaches at play, including "poke and patch," "poke and flow," "coat and poke," and "poke and release" [4]. Medical professionals are aware that innovative prevention strategies are required for the control of obesity due to its unrelenting prevalence,

despite the fact that current intervention methods for the condition yield insufficient results.

The prevalence of obesity among adults in the time period of 1975–2015 is demonstrated in Figure 1. It is evident that women are showing up in greater numbers during this time, but male and female numbers are steadily rising over time. Scientists have begun looking for solutions to the problems caused by obesity as a result of these numbers [5].

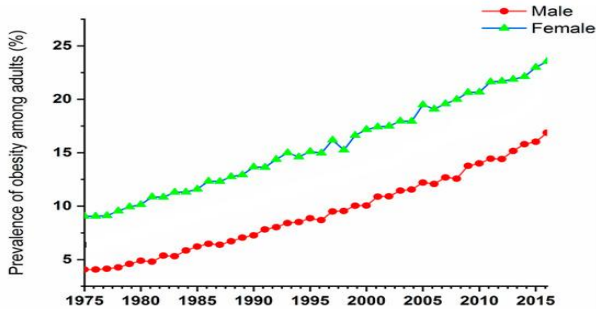


Fig 01: The frequency of obesity among individuals who are 18 years of age or older in the adult population from 1975 to 2016, according to the WHO.

The increasing global epidemic of obesity features abundant body fat, leading to multiple health dangers for both the body and metabolic system [6]. The global epidemic of obesity now affects millions of people worldwide while creating additional health problems, including cardiovascular diseases and type 2 diabetes and certain cancers that have become more widespread [7]. Five countries—the US, China, Brazil, India, and Russia—account for around a third of all cases of obesity in adults globally [8]. Transdermal administration can deliver most peptides or protein drugs that cannot be taken orally [9].

Therefore, it is no surprise that the NHS, Public Health England and the wider healthcare system are highly interested in both the prevention and treatment of obesity, though this has not translated into clear and effective pathways for either prevention or treatment. Despite this, the frequency of rotundity has continued to increase, yet the provision of weight operation services and rotundity treatment in the UK remains variable geographically and fairly limited in comparison to other European countries, most of which have a lower prevalence of obesity [10].

Furthermore, around 79% of the world's adult population aged 18 and above were overweight during that year, with the men and women comprising 39% and 40% of that population, respectively [11]. From 1975 to 2016, there was a significant increase in the worldwide occurrence of obesity, which nearly tripled. These immune cells release pro-inflammatory proteins as cell signalling molecules, which contribute to the insulin resistance commonly observed in obese individuals [12].

Conventional anti obesity therapies

The US Food and Drug Administration (FDA) has recommended five types of anti-obesity drugs: Orlistat, Phentermine/Topiramate ER, Naltrexone SR/Bupropion SR, Lorcaserin, and Liraglutide. By using the current delivery method, the efficacy of these drugs has only been found to be 3–7%. At the moment, Liraglutide is administered intravenously, whereas all other drugs are administered orally [13]. Common anti-obesity drugs, alongside their principles of action, delivery mode, and side effects, are listed in Table 1.

Table 01. Known principles, delivery modes, and side effects of common anti-obesity drugs.

ACTION PRINCIPLE	DELIVERY METHOD	NAME OF DRUG	DRAWBACKS
Reduce appetite	Oral administration	Phentermine/Topiramate ER	Taste disorders, insomnia, dizziness and constipation
		Naltrexone SR/Bupropion SR	Headache, diarrhoea and constipation Nausea, dizziness and constipation
Block the absorption of fat	Hypodermic injection	Lorcaserin	Discomfort, nausea and gastrointestinal distress
		Rimonabant	Hypertension and heart valve damage
Increase energy consumption and reduce appetite	Oral administration	Fenfluramine	Neuropsychiatric diseases, depression and dizziness
		Liraglutide	Flatulence and diarrhoea
		Orlistat	
		Sibutramine	Cerebrovascular diseases and cardiovascular

These medications have a variety of side effects, including high blood pressure, arrhythmia, nausea, dizziness, insomnia, taste failure, constipation, and so on. As a result, using these medications is frequently disallowed in patients with cardiovascular diseases, people taking other medications, and pregnant women. Orlistat is a lipase inhibitor, which checks fat absorption in the body, reduces calorie intake, and regulates weight gain. Orlistat is the world's bestselling over-the-counter (OTC) anti-obesity drug, and it is safe for teenagers [14].

Obesity can also cause male sexual dysfunction, kidney disease, irregular menstruation, and female infertility. Obesity-associated diseases are demonstrated in Figure 2.

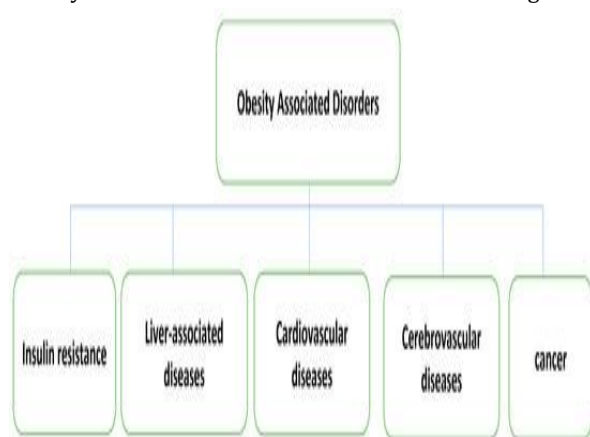


Fig 02: Chart of obesity-associated diseases.

Although these drugs are widely used for losing weight, they do have some drawbacks, including diarrhoea and flatulence. It has also been demonstrated that metformin aids in weight loss. For patients with type 2 diabetes who were obese, metformin was the first oral medication of choice. Constipation and stomach aches are among its reported side effects [15].

Advanced treatments of obesity

An imbalance between caloric intake and consumption is what leads to obesity. In addition to suppressing appetite, increasing the feeling of fullness, and preventing the absorption of nutrients, the latest medications for treating obesity also target the promotion of heat production or breakdown of fat in adipocytes [16]. The process of "browning" causes white fat cells to transform into brown-like adipocytes through various drug-related triggers [17]. The peroxisome proliferator-activated receptor (PPAR), which is responsible for regulating the storage of fatty acids and glucose metabolism, is also a crucial transcriptional regulator for the synthesis of BAT. ROSI is a type of PPAR activator that can increase insulin sensitivity in AT, liver, and skeletal muscle, and it has been utilized for diabetes treatment. Recent research has revealed that it also has a browning effect. However, taking ROSI may increase the risk of cardiovascular disease [18].

The utilization of drug delivery systems incorporating natural compounds has also found application in the realm of obesity treatment. *Salacia chinensis*, a prominent

Ayurvedic medicine, has garnered attention for its potential pharmacological effects in this context. Researchers have embarked on a study involving gold nanoparticles loaded with *S. chinensis* to investigate its anti-obesity properties [19].

These nanoparticles measured 21 nm in size and exhibited exceptional cellular uptake properties. The administration of these nanoparticles to HFD-fed rats demonstrated superior anti-obesity activity across various parameters. Consequently, this highlights the potential of transdermal delivery as an alternative route for administering natural compounds in the context of obesity therapy [20, 21].

Types of obesity

1 generalized obesity

Generalized obesity is the generalized increase in body fat, which is evenly distributed in the body, for which the BMI is usually used to diagnose it. A BMI of 30 kg/m² or more will usually diagnose obesity [22]. This kind of obesity predisposes an individual to some comorbidities, such as type 2 diabetes, heart disease, and cancer. While being a general method of diagnosis for generalized obesity, BMI fails to capture the risk that every form of fat distribution creates; hence, more specific forms of obesity types have been identified.

2 central (visceral) obesity:

Central obesity can also be referred to as visceral or abdominal obesity. It involves an accumulation of fat around the abdominal area in each internal organ. It has strong associations with metabolic syndrome, cardiovascular diseases, and insulin resistance. Visceral fat is one form of fat that is metabolically active, secreting inflammatory cytokines, enhancing insulin resistance, and thereby predisposing individuals to chronic diseases, especially cardiovascular conditions [23].

3 subcutaneous obesity:

Subcutaneous obesity refers to the deposition of extra fat just under the skin, usually in the hips, thighs, and buttocks. Though it contains extra fat, due to lower metabolic activity, subcutaneous fat is considered less dangerous compared to visceral fat. Moreover, individuals with subcutaneous obesity can also have a high risk for health complications if the total percentage of body fat is too high. This type of obesity is more common in females and less strongly associated with metabolic diseases than central obesity.

4 metabolically healthy obesity (mho)

Metabolically Healthy Obesity (MHO) describes individuals who are classified as obese according to their BMI but do not exhibit common obesity-related metabolic disorders, such as insulin resistance, hypertension, or dyslipidemia. Over time, many individuals with MHO may develop metabolic issues, particularly if preventive measures such as diet and exercise are not implemented [24].

5 metabolically obese, normal weight (monw):

MONW is a medical condition wherein a person with normal weight, with a BMI of 18.5–24.9 kg/m², may have

metabolic risk factors similar to those possessed by obese individuals, such as high blood sugar, a high level of cholesterol, and hypertension. Individuals with MONW are usually overlooked in the typical clinical setting because of their normal appearance of BMI. This calls for the reason behind the assessment of metabolic markers even in those people who do not meet the traditional definitions of obesity [25].

6 genetic obesity:

A great contribution to obesity can be made by genetic factors. Probably the most well-known genetic factor, the FTO gene stands for Fat Mass and Obesity-Associated Gene. Individuals possessing certain variants of the FTO gene may be at heightened risk of gaining weight throughout childhood and adult years. Nonetheless, environmental factors such as diet, exercise, and lifestyle determine the magnitude at which genetic tendencies develop into obesity [26, 27].

7 sarcopenic obesity:

Sarcopenic obesity refers to both the age-associated loss of muscle mass and strength combined with obesity. Special attention must be given to the treatment of sarcopenic obesity because traditional weight loss, in general, focuses only on fat reduction and may further promote muscle loss. Treatments should, therefore, be directed at fat reduction together with the preservation or increase of muscle mass through resistance training and appropriate nutrition [28].

8 hormonal obesity:

Different forms of hormonal imbalances and endocrine disorders can lead to obesity. For example, hypothyroidism, Cushing's syndrome, and polycystic ovary syndrome may all lead to metabolic dysfunctions that in turn commonly result in weight gain. Typically, obesity resulting from endocrine conditions is characterized by specific patterns of fat distribution, such as central obesity, and specific treatments are often required, including hormone therapy or medication to manage the underlying condition [29].

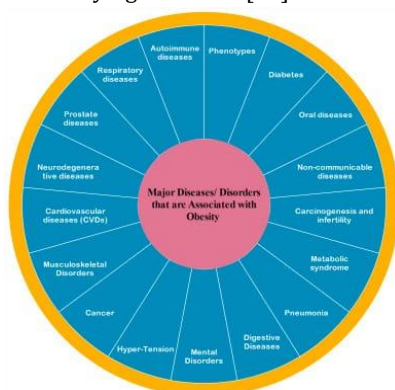


Fig 03: Specific types of diseases related to obesity.

The twin epidemics of obesity and diabetes have combined to form a major global health crisis. Several studies collected herein indicate that diabetes was also one of the most commonly considered comorbidities of obesity.

Etiology of obesity

Historically, obesity has been considered to be primarily related to an imbalance between energy intake and expenditure. However, more recent research has suggested that genetic, physiological, and behavioral factors also play a significant role in an etiology of obesity. In adults, the WHO defines 'overweight' as a BMI of 25.0 to 29.9 and 'obese' as a BMI ≥ 30.0 . Obesity is further classified into three severity levels: class I (BMI 30.0-34.9), class II (BMI 35.0-39.9) and class III (BMI ≥ 40.0) [30]. However, large individual differences exist in the percentage of body fat for a given BMI value, which can be attributed to sex, ethnicity, and age [31].

However, there is no international standard suitable for all countries or regions. The prevalence of excessive weight gain has doubled worldwide since 1980, and about a third of the global population has been determined to be obese or overweight. Obesity rate has dramatically increased in both males and females, and across all ages, with proportionally higher prevalence in older persons and women.

Energy intake

Surprisingly, no direct correlation has been reported between the prevalence of obesity and increased energy intake in developed nations, given the ready availability of highly palatable foods. Under-reporting is widely recognized as a feature of obesity, with comparisons of energy intake and expenditure in obese subjects showing a consistent shortfall in self-reported food intake of approximately 30% of the energy requirements [32].

It seems likely that environmental influences act through increasing energy intake and/or decreasing energy expenditure. There is some evidence that high-fat diets are associated with an increased risk of obesity within populations, but cross-cultural dietary studies have failed to show any consistent relationship between nutritional factors and relative weights [33]. Excessive intake of energy nutrients has been reported to increase the size and number of adipocytes at various stages of the lifespan [34].

It should be noted that in long-term weight reduction diets, it appears that both standard protein (15% protein, 55% carbohydrate) or high-protein (HP; 30% protein, 40% carbohydrate) diets result in net weight loss and improvements in cardiovascular risk factors [35].

Several studies have examined the effects of macronutrient intake at identical energy intakes on weight loss. Twin studies are often used to control for genetic differences among the participants and give insight into the true effectiveness of the intervention being studied. Also, greater-than-average caloric intake was associated with increased levels of body fat, despite likely genetic influences on both phenotypes [36].

Energy expenditure

The most variable component of energy expenditure is physical activity, representing 20–50% of total energy expenditure. A defect in metabolic mechanisms that control energy expenditure has not been described in human obesity. Longitudinal studies of Pima Indians indicate that the risk of 10-kg weight gain during a 4-year follow-up is sevenfold higher in those in the lowest tertile of relative resting metabolic rate (RMR) compared with those in the highest tertile [37].

Nevertheless, even in this population, which is predisposed to obesity, this predicts only 40% of the weight gain. In the United Kingdom, a study combining data on energy intake and physical activity in relation to the secular increase in adult obesity shows no relationship between total energy intake or fat consumption and the prevalence of obesity, but a close relationship between proxy measures of physical activity (television viewing and car ownership) [38].

Energy expenditure is composed of basal metabolic rate, the thermic effect of food, and physical activity. Physical activity can also be broken down into two distinct sub-classes: (1) activity-related thermogenesis (volitional exercise); and (2) non-activity-related exercise thermogenesis (consists of all activity that one performs that is not related to "sporting-like" exercise). Activity thermogenesis accounts for approximately 15% to 50% of total daily expenditure in the sedentary to very active populations, respectively [39].

A sedentary lifestyle is commonly mentioned as a significant cause of the mounting prevalence of obesity. In a recent study conducted by Slentz et, researchers affirmed that those individuals who partake in a modest exercise program similar to the ones suggested by the Centre's for Disease Control and the American College of Sports Medicine (e.g., at least 30 minutes of physical activity).

Environmental factors of obesity in adults:

The environmental factors are major contributors to increasing rates of obesity in the world today. Among the most critical environmental influences on obesity, those related to the built environment stand at the top (40). Urbanization came along with changing city planning and, consequently, led to lower levels of physical activity due to more people living in areas without easy access to parks and recreational facilities or places that can be used safely for walking [41]. Areas where walkability is greater or where recreational facilities are more accessible have higher records of lower obesity rates, thus indicating how urban planning can result in healthy living.

The nutritional environment is another formidable environmental factor. Over the past decades, foods that are nutritionally unhealthy and calorie-dense have become much more accessible, available, and affordable. Research has underlined just how much food marketing and the pervasive availability of fast-food breed less-than-

healthy eating and weight gain patterns, especially in neighbourhoods where healthier options are not as accessible. Fig 04.

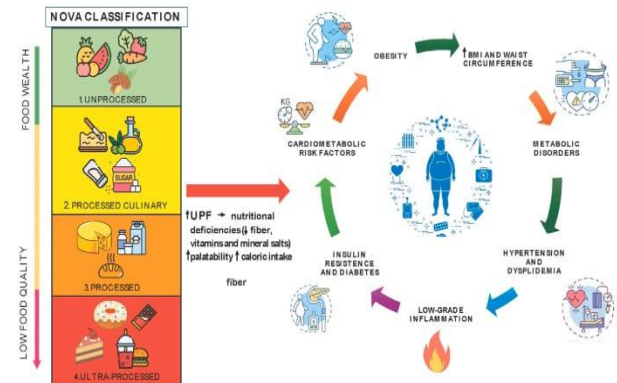


Fig 04: The relationship between Ultra-Processed Food (UPF) foods and obesity. Source licensed under CC BY 4.0. The socioeconomic variables also play a vital role in obesity. The lower-income population is more vulnerable because they have a low availability of healthy food stores and recreational areas. Lower economic communities also tend to have much higher levels of life stress and food security that promote unhealthy eating and physical inactivity.

Treatment of obesity:

Your healthcare provider will work with you to find a weight loss plan that works for you. Since everyone is different, it may take some trial and error to figure out **which therapies work best:**

Changing what you eat:

You're unique. That means you should tailor any change in what you eat to what works for you. There are ways to make meals packed with healthy food.

Building activity into your day:

Activity burns off calories, and there are many ways to boost your activity.

Mental health support:

Counselling, support groups and cognitive behavioral therapy (CBT) can help support positive changes. They can also help you manage stress and address emotional and psychological factors.

Physical control:

Obesity is primarily managed through dieting and physical activity. Obese and overweight people must follow a strict diet plan and engage in strenuous exercise. Regular diet program maintenance is typically challenging, and in the majority of cases, a person must adhere to this lifestyle indefinitely

Public health and clinical guidelines on treatment for obesity generally consider the degree of overweight, health risk factors, and comorbid conditions in identifying the most appropriate treatment for an individual. Obesity is a treatable disease that can be managed by either physical or therapeutic control, as discussed briefly below. Different obesity treatments are illustrated in Figure 5, including classical treatment techniques using natural

products and advanced techniques that include different DDSs.

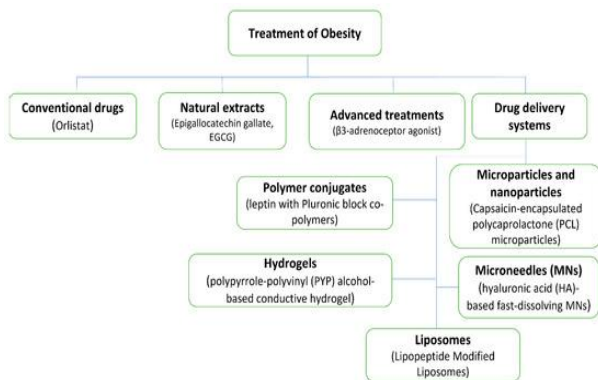


Fig 05: Obesity treatment approaches chart.

Public health and clinical guidelines on treatment for obesity generally consider the degree of overweight, health risk factors, and comorbid conditions in identifying the most appropriate treatment for an individual. Evidence suggests that even without reaching ideal weight, a moderate amount of weight loss can be beneficial in terms of reducing levels of some risk factors, such as blood pressure.

Social and economic issues

Social and economic factors are linked to obesity. It's hard to avoid obesity if you don't have safe areas to walk or exercise. You may not have learned healthy ways of cooking. Or you may not have access to healthier foods.

- **Age:**
Obesity can occur at any age, even in young children. But as you age, hormonal changes and a less active lifestyle increase your risk of obesity. The amount of muscle in your body also tends to decrease with age. Lower muscle mass often leads to a decrease in metabolism.
- **Other factors:**
 - Pregnancy:**
Weight gain is common during pregnancy. Some women find this weight difficult to lose after the baby is born. This weight gain may contribute to the development of obesity in women.
 - Quitting smoking:**
Quitting smoking is often associated with weight gain. And for some, it can lead to enough weight gain to qualify as obesity. Often, this happens as people use food to cope with smoking withdrawal.
 - Lack of sleep:**
Not getting enough sleep can cause changes in hormones that increase appetite. So can getting too much sleep.
 - Stress:**
Many external factors that affect mood and well-being may contribute to obesity. People often seek more high-calorie food during stressful situations.

Microbiome:

The make-up of your gut bacteria is affected by what you eat and may contribute to weight gain or trouble losing weight.

Prevention

Preventing obesity is easier than treating it once it's taken hold. That's because your body manages your body mass by shifting gears as it balances your hunger signals against the amount of energy you use from your daily activity.

- **Add physical activity:** Alternatively, consider what you might do to spend an extra 150 calories in a day by finding an activity that's right for you and your fitness level.
- **Shop intentionally:** Stock your home with healthy foods and save sweets and treats for special occasions when you go out.
- **Cultivate overall wellness:**
Reduce your screen time, go outside and get some fresh air. Manage your stress and try to get adequate sleep to keep your hormone levels in check.

Risk factors

Obesity often results from a combination of causes and contributing factors:

- **Family inheritance and influences:**
The genes you inherit from your parents may affect the amount of body fat you store, and where that fat is distributed. Genetics also may play a role in how efficiently your body converts food into energy, how your body regulates your appetite and how your body burns calories during exercise.
- **Lifestyle choices: Unhealthy diet:**
A diet that's high in calories, lacking in fruits and vegetables, full of fast food, and laden with high-calorie beverages and oversized portions contributes to weight gain.
- **Liquid calories:**
People can drink many calories without feeling full, especially calories from alcohol. Other high-calorie beverages, such as sugared soft drinks, can contribute to weight gain.
- **Inactivity:**
If you have an inactive lifestyle, you can easily take in more calories every day than in your burn through exercise and routine daily activities. Looking at computer, tablet and phone screens is inactivity.

Causes

The studies from family and twin studies showed that around 40-70% of the obesity variation in humans results from genetic factors. The low predictive power may be due to the situation that gene-gene, gene-environment, and epigenetic interactions have not been thoroughly identified using the current methods based on population genetics. Many obesity associated genes have been

identified to be involved in energy homeostasis-regulating pathways.



Fig 06: Factors often leading to adult overweightness/obesity.

Genetic causes of obesity can be broadly classified as monogenic causes that result from a single gene mutation, primarily located in the leptin-melanocortin pathway. 2) Syndromic obesity is severe obesity that results from neurodevelopmental abnormalities and other organ/system malformations. 3) Polygenic obesity is caused by the cumulative contribution of many genes. These conditions rely on the conventional current health recommendations that an energy imbalance between calories consumed and expended is the key cause of obesity, and present circumstances under which traditional weight management methods may not help.

On the most basic level, obesity happens when you consume more calories than your body can use. Many things may play a role in why you may eat more food than your body needs:

- **Certain medications:**
Medications you take to treat other conditions may contribute to weight gain. Examples are antidepressants, steroids, anti-seizure medications, diabetes medications and beta-blockers
- **Disability:**
Adults and children with physical and learning disabilities are most at risk for obesity.
- **Eating habits:**
Consuming more calories than your body needs, eating ultra-processed food, high-sugar foods and drinks, and foods with high amounts of saturated fat may cause overweight.
- **Genetics:**
Research shows people with obesity carry specific genes that affect appetite. It's not clear if people with overweight have the same genetic makeup.
- **Lack of sleep:**
Missing out on at least seven hours of sleep can affect the hormones that keep hunger urges under control.
- **Stress:**
Your brain and body react to stress by making more hormones like cortisol that manage hunger, which your body stores as extra fat. Although there are genetic, behavioral, metabolic and hormonal influences on body weight, obesity occurs

when you take in more calories than you burn through typical daily activities and exercise. Your body stores these excess calories as fat.

Symptoms:

While obesity is a disease, it doesn't cause specific symptoms. A healthcare provider may define obesity by calculating your:

Body mass index:

The BMI measures average body weight against average body height. Healthcare providers use BMI to classify obesity.

Body shape:

Providers may measure your waist circumference.

BMI classifications:

Healthcare providers classify obesity by your BMI. There are three general classes of obesity that providers use to decide what steps you can take to lose weight. Those classes are:

Class I obesity:

BMI 30 to less than 35 kg/m² (kilograms per square meter).

Class II obesity:

BMI 35 to less than 40 kg/m².

Class III obesity:

BMI 40+ kg/m².

Table 02: BMI classifications

BMI	WEIGHT STATUS
Below 18.5	Under weight
18.5-24.9	Healthy
25.0-29.9	Over weight
30.0 and higher	Obesity

Waist circumference: Where you carry extra weight may be a sign that you have a higher risk of health issues that obesity may cause. The U.S. Centre's for Disease Control and Prevention (CDC) say a waist circumference of more than 35 inches in females or 40 inches in males can be a risk factor for cardiovascular disease or Type 2 diabetes.

Future perspectives

Obesity is a multifactorial, chronic metabolic disorder characterized by excessive accumulation of adipose tissue resulting from an imbalance between energy intake and expenditure. It has emerged as one of the most pressing global health concerns, significantly contributing to the burden of non-communicable diseases such as type 2 diabetes mellitus, cardiovascular diseases, osteoarthritis, and certain cancers. Despite considerable advances in understanding the pathophysiology of obesity, its effective management remains a major clinical challenge due to the complexity of appetite regulation, energy homeostasis, and behavioral factors.

These challenges have prompted a paradigm shift towards the development of innovative drug formulations and advanced delivery systems that can improve therapeutic outcomes, enhance patient adherence, and minimize

toxicity. Emerging technologies such as nanocarriers, oral peptide formulations, long-acting injectable systems, and targeted delivery strategies are paving the way toward precision and personalized obesity management.

Conclusion

Emerging drug formulation and delivery technologies have revolutionized the therapeutic landscape of obesity management. By addressing the limitations of conventional treatments—such as poor bioavailability, frequent dosing, and systemic adverse effects—innovative platforms including nanocarriers, oral peptide formulations, long-acting depots, and targeted delivery systems offer superior efficacy and improved patient adherence. These advanced technologies facilitate controlled, sustained, and site-specific drug release, ultimately enhancing treatment safety and clinical outcomes. Continued research and clinical translation of these systems are expected to pave the way for next-generation, patient-centered obesity therapies.

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