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Exploring the Relationship Between Obesity and Metabolic Diseases: A Review of Current Treatments.

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Abstract

Obesity is a chronic and complex disease characterised by excessive accumulation of body fat and commonly assessed using the Body Mass Index (BMI). Over one billion people worldwide suffer from obesity, which is defined as having a BMI of 30 or more and presents major public health issues. The chance of having a number of comorbidities, such as type 2 diabetes (T2D), non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), chronic renal disease, and several types of cancer, is greatly increased by obesity. Numerous genetic, environmental, and behavioural variables, including poor diet, sedentary lifestyle, and socioeconomic position, interact intricately to determine its development. At the molecular level, obesity is linked to a number of regulatory pathways and biomarkers. These include sirtuin 1 (SIRT1), programmed cell death protein 1 (PD-1) and its ligand PD-L1, toll-like receptors (TLRs), and gut microbiota species like Akkermansia muciniphila, all of which affect immune function, inflammation, and energy metabolism. Insulin resistance, disturbed hormonal signalling, and persistent low-grade inflammation are all influenced by these pathways. Current clinical management strategies for obesity include pharmacological treatments, bariatric surgery, gut microbiota-targeted therapies (such as faecal microbiota transplantation and probiotics), psychological support, lifestyle changes (such as dietary changes and physical activity), and newer techniques like microRNA-based interventions. Long-term management of obesity is still challenging because of its recurrent nature and underlying complexity, even with the variety of therapeutic options available. In the future, there is hope for more focused, long-lasting, and efficient treatments for obesity and associated metabolic diseases through the combination of molecular insights, personalised medicine, and digital health technology.

Keywords: Obesity; Comorbidities; Metabolic disease; Bariatric surgery; Exercise

1. Introduction

Obesity is a long-term health condition caused by having too much body fat. A common way to measure it is by using the Body Mass Index (BMI), which is calculated by dividing a person's weight in kilograms by the square of their height in meters. Based on BMI, people are grouped into different categories: a BMI below 25 is considered underweight or normal, a BMI between 25 and 30 means overweight, a BMI between 30 and 35 is called moderate obesity, and a BMI of 35 or higher is considered severe obesity. These categories help doctors understand the health risks related to body weight and decide on the best treatment options. **[1]** The World Health Organisation (WHO) reports that over 1 billion people around the world are affected by obesity, including 650 million adults, 340 million teenagers, and 39 million children. WHO also estimates that by the year 2025, obesity will be responsible for around 167 million new cases of health-related conditions. [**2]** Environmental and genetic factors work together to impact the prevalence of obesity. The development of obesity can be significantly influenced by a person's sex, ethnicity, degree of physical activity, eating habits, and socioeconomic situation. **[3]** A Japanese study found that obesity is more common in men than in women, with rates of 27.2% and 10.6%, respectively. Additionally, factors like marital status, participation in welfare programs, and current financial condition are associated with obesity in women, whereas these factors do not appear to have the same effect on men.

Obesity can be caused by various factors, including lack of physical activity, excessive food intake, economic status, environmental influences, and genetic predisposition. **[5]**. For example, during the COVID-19 pandemic, reduced socioeconomic activities, along with increased sedentary behaviour and higher food intake, contributed to a rise in obesity rates. **[6]** The development and progression of obesity can be affected by certain genes, such as those responsible for producing leptin and its receptor, as well as genes like MC4R, PCSK1, POMC, KSR2, and ADCY3. These genes play important roles in controlling appetite, metabolism, and how the body stores fat. **[7]** For example, mutations of the ADCY3 gene cause obesity in children from consanguineous Pakistani families, while heterozygous mutations are associated with the severity of obesity in children of European–American descent **[8]**. A mutation in the ADCY3 gene has also been closely associated with an increased risk of type 2 diabetes (T2D) and obesity in the Greenlandic population. **[9]**

Various other metabolic health issues, including type 2 diabetes (T2D), non-alcoholic fatty liver disease (NAFLD), heart and blood vessel diseases (CVDs), chronic kidney disease (CKD), and some forms of cancer, are frequently associated with obesity. **[10, 11]** Additionally, in patients infected with COVID-19, obesity has been reported to be substantially associated with increased severity and a higher chance of death. **[12]** Several inflammatory substances, such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), are released by fat tissue. These substances significantly contribute to issues with the body's energy processing and utilisation, resulting in metabolic disorders. Obesity can cause several other health problems, such as damage to the cells lining blood vessels and fat build-up in organs that don’t normally store fat. The following sections go over the different factors involved in health issues related to obesity. Then, the molecular pathways that contribute to obesity are discussed. Lastly, the current methods for managing and treating obesity are summarised.

2. Obesity, Its Comorbidities, and Associated Factors

Obesity contributes to the onset of various chronic health conditions, including chronic kidney disease (CKD), cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), type 2 diabetes (T2D), and certain cancers such as hepatocellular carcinoma (HCC), both directly and indirectly. As an example, NAFLD impacts as many as 70–90% of those who are obese and is closely associated with a high body mass index (BMI of 35 or greater). **[13]** Health problems linked to obesity, such as inflammation, insulin resistance, and metabolic issues, heighten the risk of illness and mortality related to these conditions. This section examines a number of frequent health issues associated with obesity, as well as the underlying causes.

2.1. Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) represents a significant worldwide health concern, impacting approximately 13.4% of the global population. Common symptoms experienced by individuals with CKD include sleep disturbances, fatigue or weakness, pain, and skin itching. **[14]** CKD can advance to end-stage kidney disease, which usually necessitates treatments such as dialysis or a kidney transplant. **[15]** Obesity contributes to the deterioration of CKD by causing fat accumulation in the kidneys, impairing their waste filtration efficiency, and resulting in protein presence in urine (albuminuria). **[16]** Obesity-related inflammation, occurring both locally and systemically, as well as insulin resistance, tissue scarring (fibrogenesis), and gut microbiome imbalances, all play a role in the onset and advancement of CKD. **[17, 18, 19]** People who are overweight or obese and also have metabolic issues are at a greater risk of developing chronic kidney disease (CKD). **[20]** That's why it's important for those with obesity to manage their weight and follow a healthy diet to help reduce this risk.

2.2. Cardiovascular disease (CVD)

Factors associated with obesity—including irregular cholesterol levels (dyslipidemia), hypertension, insulin resistance, issues with blood vessel function, and sleep disorders—can heighten the risk of developing cardiovascular disease (CVD). **[21, 22]** Health issues associated with obesity, such as chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NAFLD), can increase the likelihood of cardiovascular disease (CVD). **[23, 24]** For example, the chronic, low-grade inflammation in fat and liver tissues caused by obesity can alter the levels of crucial substances like adiponectin and high-density lipoprotein (HDL). These alterations impact the body's energy management and can harm the endothelial lining of blood vessels, thereby elevating heart disease risk. **[25]** Adipose tissue produces a variety of signalling molecules known as adipocytokines, such as leptin, resistin, visfatin, TNF-α, and IL-6. **[26]** These molecules have distinct functions in the development of cardiovascular disease (CVD). Certain adipocytokines, such as omentin and adiponectin, derived from visceral fat (the fat surrounding the organs), exhibit anti-inflammatory properties. **[27]** They assist in controlling nitric oxide production in blood vessel cells and help reduce inflammation and keep the blood vessels from becoming stiff or clogged. However, certain molecules such as resistin and TNF-α are associated with insulin resistance, particularly in cases of obesity and type 2 diabetes. Another important molecule, IL-6, plays a role in the accumulation of fat in the heart. Studies indicate that inhibiting IL-6 or its receptor can reduce the likelihood of developing coronary artery disease, atrial fibrillation, and type 2 diabetes. **[28]**

2.3. Non-alcoholic Liver Disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver condition, impacting more than 25% of the global population. **[29, 30].** NAFLD enhances the risk of liver cancer (also known as hepatocellular carcinoma or HCC), cardiovascular disease (CVD), and type 2 diabetes (T2D). Even in individuals who are metabolically fit, a major study indicated that being overweight or obese is substantially associated with an increased risk of developing non-alcoholic fatty liver disease (NAFLD). Overweight people in this study had a risk that was more than twice as high, while obese people had a risk that was more than three times higher. **[31].** A prediction model based on obesity and type 2 diabetes (T2D) rates predicts that many countries will see an increase in the number of persons with NAFLD and its more severe form, NASH. **[32].** NAFLD and its development into non-alcoholic steatohepatitis (NASH), a more severe illness, can be caused by a number of obesity-related causes. These include issues with insulin resistance, chronic inflammation, subcutaneous white fat tissue (scWAT) **[33]**, gut bacterial imbalances, and abnormal energy metabolism. **[34]**

Even those with a normal body weight (thin NAFLD patients) are at a higher risk of liver-related death than those who are overweight or obese, despite the fact that obesity is a significant cause of NAFLD. **[35]** In addition to having less liver scarring (fibrosis) and a reduced incidence of type 2 diabetes, these slender patients usually don't have significant abdominal fat. Nonetheless, they frequently struggle with

dyslipidaemia, or elevated blood fat. **[36]**

2.4. Type 2-Diabetes

The most common type of diabetes is type 2 diabetes (T2D), a chronic illness characterised by high blood sugar levels. Insulin resistance is the main underlying mechanism of type 2 diabetes (T2D), as opposed to type 1 diabetes (T1D), which is characterised by insulin insufficiency brought on by the death of pancreatic β-cells. **[37]** Over 21.7 million people worldwide suffer from type 2 diabetes (T2D), which claimed about 1.5 million lives in 2019. **[38].** Some factors, including physical inactivity, smoking, poor diet, and genetic susceptibility, contribute to the start and progression of type 2 diabetes (T2D). Obesity and insulin resistance can promote hypertrophy of the pancreatic islets and lead to morphological and functional alterations in both α- and β-cells, such as disarray and cell death. Nevertheless, fasting and T2D management therapies can lessen these effects. **[39, 40]**

2.5. Cancers

It has been established that obesity has a major role in accelerating the development of several malignancies, including breast cancer. **[41, 42]** The development of numerous cancer types is closely associated with insulin resistance, adipose tissue inflammation, and the presence of tumor-promoting growth factors such as fibroblast growth factor 1 (FGF1). **[41]** Additionally, obesity can impair the body's immune response against tumors. For example, in cases of non-alcoholic fatty liver disease (NAFLD)-associated hepatocellular carcinoma (HCC) caused by a high-fat diet, the buildup of cholesterol in the liver as a result of obesity might specifically inhibit the anti-tumor activity of natural killer T (NKT) cells. **[43]** Molecular analysis further reveals that lipid peroxide accumulates in NKT cells, reducing their ability to kill tumor cells. This effect is driven by excessive cholesterol buildup in hepatocytes, regulated by sterol regulatory element-binding protein 2 (SREBP2)**. [43]**

All things considered, obesity might accelerate the development of the diseases indicated above by encouraging metabolic syndrome, chronic inflammation, abnormalities in the gut microbiota, and vascular endothelial cell dysfunction. Obesity also increases the likelihood of developing COVID-19 and other illnesses. According to one study, children and adolescents with COVID-19 who are obese had a higher chance of dying and being admitted to the hospital. Notably, those who are obese and have a body mass index (BMI) of more than 40 kg/m² have a far higher death risk. **[44]**

3. Molecular Targets for Obesity Treatment

3.1. Inflammation-Associated Molecules

Increased serum levels of inflammatory agents, such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and resistin, are frequently seen in obese or overweight people. **[45, 46, 47]** Insulin resistance and other metabolic diseases frequently coexist with these increased inflammatory markers. On the other hand, adiponectin, an adipokine that reduces inflammation, is frequently found in lower amounts in obese patients. Chronic inflammation in adipose tissue, fueled by the secretion of adipokines, cytokines, and chemokines, is a characteristic of obesity. Both invading immune cells and malfunctioning adipocytes within the adipose tissue release these inflammatory mediators. **[48]** For example, during adipogenesis, adipocytes may release resistin, which can lead to the development of insulin resistance. **[47]**

Leukocyte infiltration and increased vascular permeability are important contributors to the systemic inflammation brought on by obesity. In the white adipose tissue (WAT) of diet-induced obese mice, for instance, the administration of the neutrophil elastase inhibitor GW311616A dramatically lowers vascular leakage, leukocyte infiltration, and the expression of proinflammatory cytokines. **[49]** Adipogenesis and inflammatory markers like TNF-α and IL-6 are linked to the production of adhesion molecules like vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1). **[50]**

Low molecular weight hyaluronan (HA) molecules (15–40 kDa) are more prevalent in the bloodstream of obese people. Higher amounts of pro-inflammatory cytokines, such as interleukin-1β, interleukin-8 , and monocyte chemoattractant protein-1 (MCP-1, also called CCL2), are produced by peripheral blood monocytes in response to this rise. **[51]**

3.2. Metabolic Syndrome-Associated Molecules

A number of disorders, such as insulin resistance, dyslipidaemia, high blood pressure, and abdominal obesity, are collectively referred to as metabolic syndrome. **[52,53]** One important metabolic regulator that is essential for regulating inflammation and fat buildup is sirtuin 1 (SIRT1). SIRT1 regulates the production of peroxisome proliferator-activated receptor alpha (PPAR-α) and sterol regulatory element-binding transcription factor 1c (SREBF1c) in adipocytes, both of which are essential for preserving mitochondrial function and general metabolic homeostasis **[54]** In addition, the expression of molecules including leptin, adiponectin, and matrix metalloproteinases is regulated by SIRT1-mediated signalling pathways **[54]** Upregulating the expression of SIRT1 in WAT in mice with high-fat diet (HFD)-induced obesity can ameliorate weight gain **[55]** In a number of illnesses, including obesity, diabetes, and cardiovascular disorders, SIRT1 activation is crucial for lowering oxidative stress, inflammation, and cell death. For example, improved insulin sensitivity has been associated with increased SIRT1 expression in cardiac muscle cells. **[56]**

3.3. Fatty Acid Metabolism-Associated Molecules

The development of illnesses, particularly obesity-related malignancies, is significantly influenced by fatty acid metabolism. To reduce inflammation, monounsaturated fatty acids can interact with peroxisome proliferator-activated receptors (PPARs) and G protein-coupled receptors (like GPR120). They accomplish this by inhibiting the polarisation of M1 macrophages and modifying pathways such as the NLRP3 inflammasome and NF-κB. **[57]** Conversely, a study with a median follow-up of 11 years discovered that Chinese individuals who consume more medium-chain saturated fatty acids (MCSFAs) as opposed to total saturated fatty acids (TSFAs) are at a higher risk of being overweight or obese. **[58]** Consuming saturated fatty acids (SFAs) also raises serum ceramide levels and causes liver fat to accumulate, according to a clinical investigation (NCT02211612). Polyunsaturated fatty acid (PUFA) consumption, on the other hand, has been demonstrated to decrease ceramide levels, lessen hyperlipidaemia, and stop the accumulation of liver fat after excessive energy intake in obese people. **[59]**

3.4. Immune Checkpoints

In those who are overweight or obese, there is a positive correlation between visceral fat accumulation and the expression of programmed death-ligand 1 (PD-L1) in adipose tissue. Conditional deletion of PD-L1 in dendritic cells (DCs) causes mice to gain more weight and develop diet-induced obesity more quickly. **[60]** Another study shows that the presence of PD-L1's receptor, programmed cell death protein 1 (PD-1), in visceral WAT is associated with PD-L1 expression in mouse white adipose tissue (WAT) **[61]** Type 2 innate lymphoid cells in adipose tissue exhibit elevated PD-1 levels, which are linked to metabolic dysfunction. The recruitment and activation of M1 macrophages with elevated PD-L1 expression is linked to this impact. **[62]**

3.5. Exercise-Associated Signaling Molecules

A clinical study (NCT02753231) found that taking a low-to-moderate intensity physical education class (LIPE) either alone or in conjunction with a high-intensity class has a significant impact on the expression of a number of immune-regulatory and inflammatory markers. These consist of fibroblast growth factor 6 (FGF6), C-C motif chemokine ligands 5 (CCL5), 11 (CCL11), 13 (CCL13), 18 (CCL18), and C-X-C motif chemokine ligand 13 (CXCL13 or BLC)**. [63]** Exercise also increases the M2 macrophage marker CD163 while decreasing the expression of TNF-α and the macrophage marker F4/80 in the adipose tissue of mice fed a high-fat diet (HFD), according to a mouse study. This implies that within the adipose tissue, pro-

inflammatory M1 macrophages give way to anti-inflammatory M2 macrophages. **[64]**

Exercise also helps prevent oxidative stress and mitochondrial dysfunction associated with obesity **[65]** by altering certain lipid profiles, including acylcarnitines, diacylglycerols, ceramides, and cardiolipins. **[66]**

3.6. Toll-like Receptors

Due to their ability to identify pathogen-associated molecular patterns (PAMPs) originating from diverse microbiomes, toll-like receptors (TLRs) are essential elements of the immune system, especially in the innate immune response **[67]** Obesity in overweight people has been strongly associated with specific genetic variations of the TLR-2 gene, particularly in exons 3 and 4 **[68]** TLR4 deficiency reduces obesity caused by a high-fat diet (HFD) in young mice (≤6 months). However, obesity and chronic low-grade inflammation develop spontaneously in 18-month-old TLR4 knockout (TLR4-/-) mice **[69]** According to a different study, TLR4-/- mice fed a high-fat diet have a higher subcutaneous-to-visceral fat ratio and a lower M1/M2 macrophage ratio and lower levels of insulin resistance, oxidative stress, and chronic inflammation. **[70]** These effects are associated with changes in adipose tissue's mitochondrial metabolism. The development of metabolic diseases linked to obesity is also linked to TLRs, including TLR4 and TLR9. **[71, 72]**

3.7. Intestinal Barrier-Associated Molecules

Gut microbiota plays a critical role in obesity Leakage of the gut barrier is commonly found during gut microbiota dysbiosis. Some gut microbial species, such as the mucin-degrading bacterium Akkermansia muciniphila, are involved in the protection of permeabilization of the gut barrier and systemic inflammation **[73]** These bacteria also contribute to intestinal stem cell-mediated epithelial cell development and a decreased population of B cells in the intestine **[73, 74]** In addition, treatment of A. muciniphila can decrease serum levels of inflammatory cytokines and lipid overload and increase fatty acid oxidation in adipocytes. **[75]** Overall, a variety of molecules and signalling pathways have a role in the emergence of obesity and its associated consequences, which makes them attractive targets for treatment.

4. Clinical Management of Obesity

Obesity is a major contributing factor to many diseases at different stages of obesity ; therefore, it is critically important to prevent and treat obesity. Here, we review some commonly applied strategies in obesity prevention and treatment. In addition, the underlying mechanism of each treatment is also discussed.

4.1. Exercise

According to a meta-analysis, exercise, especially aerobic activity, significantly lowers levels of N-terminal prohormone B-type natriuretic peptide (BNP) in heart failure patients, irrespective of their obesity status. **[76]** In another study, a 12-week aerobic and resistance training exercise program significantly reduced the negative effects of β-amyloid plaques on brain function in obese rats treated with β-amyloid, and the intervention also improved short-term memory, muscle endurance, and cardiopulmonary performance. **[77]** This exercise program also increased the expression of several brain-related proteins in the hippocampus and cerebral cortex, such as FNDC5 (fibronectin type III domain-containing protein 5) and BDNF (brain-derived neurotrophic factor).

2. Diets

4.2.1. Carbohydrate-Restricted Diets

Diets that contain more than 45% carbs are generally classified as high-carbohydrate diets. **[78]** Moderately low carbohydrate diets (MCD), low carbohydrate diets (LCD), and very low carbohydrate diets (VLCD) are the typical classifications for carbohydrate-restricted diets, where carbs make up 26–45%, 10–25%, and less than 10% of daily calories, respectively. Both MCD and LCD are dietary approaches that are advised for weight loss in persons who are overweight or obese in South Korea. **[79]** Even though moderate carbohydrate restriction can help overweight or obese people with type 2 diabetes (T2D) lose weight, results from a recent clinical trial (NCT03814694) show that neither overall cognitive function nor health-related quality of life are significantly improved. **[80]**

4.2.2. Low-Fat Diet

A low-fat diet (LFD) has been demonstrated to lower total cholesterol (TC) levels in obese people; however, triglycerides (TG) are not much impacted. However, compared to either intervention alone, combining an LFD with moderate-intensity aerobic activity training (MIAET) results in significant reductions in both TC and TG as well as improvements in depressed symptoms. **[81]**

4.2.3. Fiber Diet

Dietary fibre, which is mostly made up of different polysaccharides, is essential for lowering obesity and the health problems that come with it **[82]** Mechanistically, a high-fibre diet can affect the production of gut hormones like peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), as well as regulate hunger, produce secondary bile acids, regulate energy metabolism, and affect insulin sensitivity. Participants in a 12-week trial who consumed rye-based goods, which are high in fibre and whole grain, saw larger drops in body weight, body fat, and C-reactive protein levels than those who consumed wheat-based products. **[83]**

4.2.4. Mediterranean Diet

Healthy fats, whole grains, fruits, vegetables, fish, nuts, and legumes are all part of the Mediterranean diet (MedDiet), which aids in weight loss and reduces health issues associated with obesity. **[84, 85, 86]** The benefits of a low-fat diet (LFD) and the Mediterranean diet (MedDiet) on obese teenagers with non-alcoholic fatty liver disease (NAFLD) were compared in a clinical research study (NCT04845373). About 40% of calories on the MedDiet come from carbohydrates, 35%–40% from fats (less than 10% from saturated fats), and 20% from protein. Along with consuming walnuts and olive oil every day, it also entails eating fish and beans two to three times per week. 50–60% of calories on the LFD come from carbohydrates, 20% come from protein, and less than 30% come from fats (including less than 10% saturated fat) **[86].** Both diets resulted in notable decreases in insulin resistance, liver fat, and liver enzyme levels after 12 weeks. In contrast to the LFD group, the MedDiet group exhibited stronger antioxidant activity, with higher levels of paraoxonase-1 and glutathione peroxidase and lower levels of aspartate aminotransferase (AST) ($p < 0.05$). Furthermore, the LFD decreased IL-6 levels, but the MedDiet decreased C-reactive protein (CRP) levels. According to a different meta-analysis, sticking to the MedDiet is associated with a decreased chance of gaining weight over the course of five years and becoming overweight or obese **[87]** Examples of these include the following: Overall, metabolic problems associated with obesity are improved by adequate energy limiting and the consumption of low-fat and high-fibre diets.

4.3. Bariatric Surgery

Bariatric surgery (BS) has been shown to be a successful treatment for extreme obesity (BMI ≥ 35), improving patients' quality of life and lowering obesity-related health issues **[88]**. Quality of life following surgery is significantly influenced by weight loss, including overall weight loss and final BMI **[89]**. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the two most popular forms of bariatric surgery **[90]**. For example, in individuals with type 2 diabetes (T2D) who are overweight or obese, laparoscopic gastric bypass, or SG, can dramatically reduce body mass index (BMI) and improve blood sugar levels after meals. **[91]** According to certain research, obese people with type 2 diabetes (T2D) who undergo Roux-en-Y gastric bypass (RYGB) lose more weight than those who undergo sleeve gastrectomy (SG). However, following surgery, the percentages of T2D remission are comparable for both surgeries. **[92, 93, 94]** Reduced energy absorption, enhanced gut hormone release, and improved gut microbial balance are some of the ways that bariatric surgery (BS) helps treat obesity and associated health problems. Both sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) alter the levels of gut hormones such as ghrelin, glucagon-like peptide-1 (GLP-1), and peptide YY (PYY) in order to induce weight loss. RYGB increased GLP-1 and PYY levels 26 and 52 weeks post-surgery, according to one study. In contrast, SG decreased ghrelin levels relative to pre-surgery levels and solely raised PYY and GLP-1 after 26 weeks. **[95]** Variable bariatric surgery (BS) techniques may cause variable levels of gut hormones, which could affect how well people lose weight. Following BS, an examination of the gut microbiota in obese people showed an increase in Bacteroides and a drop in Blautia species abundance. Furthermore, it was discovered that a greater BMI was positively connected with a larger Blautia to Bacteroides ratio. **[96]** In general, bariatric surgery (BS) improves the balance of gut bacteria, increases the release of gut hormones, and limits or decreases energy absorption in order to treat obesity.

4.4. Medicines

In conclusion, the FDA has authorised a number of anti-obesity drugs that help people lose weight through a variety of methods. These include opioid receptor antagonists in combination with dopamine/norepinephrine reuptake inhibitors (e.g., naltrexone/bupropion), noradrenergic agonists (e.g., phentermine), serotonin-norepinephrine-dopamine releasing agents (e.g., diethylpropion), lipase inhibitors (e.g., orlistat), GLP-1 analogues (e.g., liraglutide and semaglutide), melanocortin-4 receptor agonists (e.g., setmelanotide), and phentermine combined with a GABA agonist (e.g., topiramate extended-release). By regulating hunger, metabolism, and fat absorption, these drugs aid in the management of obesity. **[97,98]** A prior review covered the mechanisms of action of various anti-obesity drugs. **[98]** Some of these drugs, like diethylpropion in Europe, are less often prescribed or have been discontinued because of negative side effects. Clinical trials are actively testing a number of novel therapy alternatives. A 4-week subcutaneous infusion of hormones such as PYY, GLP-1, and oxyntomodulin (OXM) at specified levels, for example, dramatically decreased body weight and enhanced glucose tolerance in obese diabetic patients, according to a single-blind trial. **[99]**

4.5. Management of Gut Microbiota

Obesity and other metabolic diseases are significantly influenced by gut microbiota **[100, 101].** According to research, gut microbiota can affect insulin resistance, systemic inflammation, intestinal hormone secretion, gut permeability, energy balance, and nutrition metabolism. **[102,103]** Obesity and other metabolic diseases are significantly influenced by gut microbiota. **[100,101]** According to research, gut microbiota can affect insulin resistance, systemic inflammation, intestinal hormone secretion, gut permeability, energy balance, and nutrition metabolism. **[104,105],** probiotics (e.g., Bifidobacterium and Lacticaseibacillus) **[106,107],** prebiotics, and synbiotics (containing both probiotic and prebiotic components).

Weekly faecal microbiota transplantation (FMT) capsules from healthy lean donors administered to obese adults for 12 weeks produced successful gut microbiota engraftment in the majority of recipients without causing any side effects, according to a clinical trial conducted at a U.S. academic medical centre (NCT02530385) **[108]** For three months, daily oral supplementation of live or pasteurised Akkermansia muciniphila was safe and well-tolerated, according to another trial (NCT02637115). **[109]** In comparison to a placebo, pasteurised A. muciniphila treatment decreased total cholesterol, increased insulin sensitivity, and marginally decreased body weight ($p = 0.091$). Without changing the gut microbial profile, it also reduced blood indicators of inflammation and liver damage. Adiponectin expression was up while body weight, visceral fat, and waist circumference were significantly decreased after 12 weeks of probiotic supplementation with Lactobacillus curvatus HY7601 and Lactobacillus plantarum KY1032 (10^10 CFUs) in comparison to the placebo group. **[110]** The gut microbiota profile is changed by this treatment, with the Prevotellaceae and Selenomonadaceae families becoming less abundant and the Bifidobacteriaceae and Akkermansiaceae families becoming more abundant. Taking a synbiotic supplement increases the amount of Lactobacillus and Bifidobacterium, two types of helpful bacteria. Blood glucose levels over time are negatively correlated with Lactobacillus abundance, whereas Bifidobacterium abundance is favourably correlated with obesity-related variables such as body mass, BMI, waist circumference, and body fat mass over time**. [111]**

By changing the gut microbiota, the conventional bariatric surgery (BS) procedures of sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) help lower body weight and improve insulin resistance and inflammation associated with obesity. Among these is a decline in the species Monoglobus, Eubacterium ventriosum, and Butyriciccocus **[112**] Consuming high-fibre rye meals has been shown in another study to decrease Ruminococcus levels while increasing the abundance of Agathobacter, which produces butyrate. This alteration is associated with elevated plasma butyrate levels and decreased low-grade inflammation **[113]** All things considered, recent clinical research shows how gut microbiota therapies may be used to treat obesity and associated disorders. To evaluate the efficacy of these microbiome-based treatments for obesity, more extensive clinical studies and investigation into the precise makeup of the gut microbiota are required.

4.6. Psychological Management

It has been demonstrated that psychological therapies are successful in treating mental and emotional illnesses. Obesity and its related comorbidities are also strongly correlated with depression. **[114]** One study, for example, in Germany, discovered that the prevalence of obesity and depression was 2.0% in women (95% CI: 1.3–3.0) and 1.3% in males (95% CI: 0.8–2.0) **[115]** In a different cohort study of middle-aged and older Chinese people (≥45 years), people who had both obesity and depression were more likely to acquire functional disability than people who had either condition alone or neither. **[116]** As a result, psychological management may be useful in the fight against obesity.

4.7. Micro RNA-Mediated Therapy

Small, non-coding RNA molecules known as microRNAs (miRNAs) are essential for preserving health and controlling the progression of disease. **[117]** MiRNAs are interesting targets for the treatment of obesity since recent studies have demonstrated their involvement in both obesity and the formation of fat cells (adipogenesis). **[118]** For example, miR-203 targets an apical sodium-dependent bile acid transporter to modulate bile acid balance, hence lowering aberrant lipid levels (dyslipidaemia) and obesity. **[119]** Furthermore, alterations in lifestyle can affect the levels of circulating miRNAs such as miR-99-5p and miR-100-5p, which are associated with improved glucose regulation and decreased fat formation in individuals with abdominal obesity. **[120]** Moreover, metabolic diseases like obesity, insulin resistance, and type 2 diabetes (T2D) are linked to members of the miR-29 family, including miR-29a-3p, miR-29b-3p, and miR-29c-3p. This suggests that these genes may be used as biomarkers and therapeutic targets. **[121, 122]** Treating obesity and its associated diseases, including non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and cardiovascular disease (CVD) may benefit from altering particular miRNAs. **[123, 124]**

5. Limitations and Future Perspectives

Treatment of obesity is complicated by a number of circumstances, such as low socioeconomic position, time constraints, underrecognition of the problem, and the existence of numerous comorbidities. **[125]** Furthermore, although lifestyle modifications like eating a healthier diet and exercising more are advised, they are frequently insufficient to maintain long-term weight loss because obesity is a chronic, relapsing condition **[126]** Although bariatric surgery (BS) is quite successful for people who are extremely obese **[127]**, its wider application is constrained by high expenses, restricted access to care, and worries about possible adverse effects. Similarly, incorrect usage of anti-obesity drugs might result in undesirable side effects and reduce their effectiveness. **[128]**

To effectively track the onset and course of obesity, new diagnostic and prognostic indicators are required. Fasting insulin (FI) and fasting plasma glucose (FPG), for instance, can be used to predict how well a person will react to weight loss from a low-fat or low-carb diet. **[129]** Increased FPG levels are associated with better weight reduction and maintenance outcomes, particularly when consuming diets high in fibre and whole grains or low in glycaemic load. **[130]** The management of obesity is also being improved by developments in wearable technologies. The ability of wearable sensors to monitor vital health parameters, including blood pressure, temperature, heart rate, and respiration rate, allows for the early identification of obesity-related dangers and aids in evaluating the efficacy of treatment. **[131, 132]** Better long-term results are supported by these gadgets' useful features for self-monitoring and promoting exercise. **[133]**

It's crucial to assess novel medicines in preclinical research before proceeding with clinical trials. To investigate the cellular and molecular mechanisms behind obesity and to evaluate the efficacy of prospective therapies, animal models—particularly in mice—are frequently employed. Numerous mouse models of obesity have been extensively examined in earlier studies. **[134]**

6. Summary

Obesity is a complicated disease caused by intricate interplay between genetic, lifestyle, and environmental variables; it is not just a condition of being overweight. Systemic inflammation, immunological dysregulation, and metabolic dysfunction are its hallmarks, and it dramatically raises the risk of many chronic diseases. Disease progression is influenced by important molecular factors, including gut microbiota, microRNAs, immunological checkpoints, and inflammatory cytokines. Clinical strategies for treating obesity are changing and now include bariatric operations, medicinal treatments, microbiota-based interventions, and diet and exercise regimens. The chronic nature of obesity, socioeconomic constraints, and biological resistance to weight loss, however, make long-term management challenging. In the future, preventing and treating obesity and its related consequences will require a more thorough, individualised, and multidisciplinary strategy driven by molecular insights and technology advancements.

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