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Review

Obesity and digestive diseases

Antonija Mišković [1] *, Ivana Pajić Matić [1], Damir Sauerborn [1], Ivo Matić [2], Mihovil Penavić [3], Josip Glavić [2]

[1] Department of Otolaryngology, General Hospital Dr. Josip Benčević, Slavonski Brod, Croatia

[2] Department for Anesthesiology, Reanimatology and Intensive Medicine, General Hospital Dr. Josip Benčević, Slavonski Brod, Croatia

[3] Department of Emergency Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

* Correspondence to: Antonija Mišković, Department of Otolaryngology, General Hospital Dr. Josip Benčević, Slavonski Brod, Croatia. E-mail: miskovic.antonija@gmail.com

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Abstract

Obesity is a prevalent, multifactorial disease in modern developed societies that significantly increases the risk of various noncommunicable diseases. It disrupts metabolic homeostasis by promoting excessive fat accumulation, which leads to an imbalance between proinflammatory and anti-inflammatory adipokines. As a potent endocrine organ, adipose tissue secretes adipokines that play a crucial role in metabolic regulation. Metabolic and inflammatory changes associated with obesity have a profound impact on the development and progression of digestive diseases. Dysfunction of excess adipose tissue leads to chronic low-grade inflammation, alterations in gut microbiota, and disruptions in neuroimmune signaling. These factors contribute to gastrointestinal and liver disorders, including conditions such as gastroesophageal reflux disease, non-alcoholic fatty liver disease, gallbladder disease, pancreatitis, and colorectal cancer. Metabolic disturbances associated with obesity may worsen inflammatory bowel disease and disrupt the gut-brain axis, ultimately affecting intestinal health. Obesity affects the intestinal barrier, leading to dysbiosis and immune system dysfunction. Additionally, obese patients have a higher risk of developing esophageal, liver, and pancreatic cancers. This review examines the impact of obesity on digestive diseases, highlighting its influence on gut health, inflammation, and related complications.

Keywords: adipose tissue, overweight, gastroesophageal reflux, fatty liver, intestinal diseases

Introduction

Obesity is one of the most prevalent multifactorial diseases of the modern age, characterized by the accumulation of excessive body fat. A quick and easy-to-use method to measure obesity is the body mass index (BMI), calculated by dividing a person's weight by their height squared. A BMI between 18.5 kg/m^2 and 24.9 kg/m^2 is considered normal, a BMI between 25 kg/m^2 and 29.9 kg/m^2 is classified as overweight, and a BMI of 30 kg/m^2 or higher is considered obese. Although BMI is not a direct measure of adiposity and cannot distinguish visceral from subcutaneous fat and muscles, it remains a practical standard in clinical and surveillance settings of obesity due to its non-invasive and inexpensive nature. It is estimated that overweight and obesity affect almost 60% of the adult population in the European Region, as well as 7.9% of all children under 5 years of age [1].

Obesity is linked to an increased risk for many noncommunicable diseases (NCDs), a group of non-infectious chronic diseases caused by a combination of lifestyle choices, genetic predisposition, and environmental influences. Four risk factors linked to mortality from NCDs are tobacco use, lack of exercise, excessive alcohol intake, and an unhealthy dietary pattern (Figure 1) [2]. Obesity is associated with the onset of metabolic syndrome and related conditions, such as type 2 diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, cardiovascular disease, obstructive

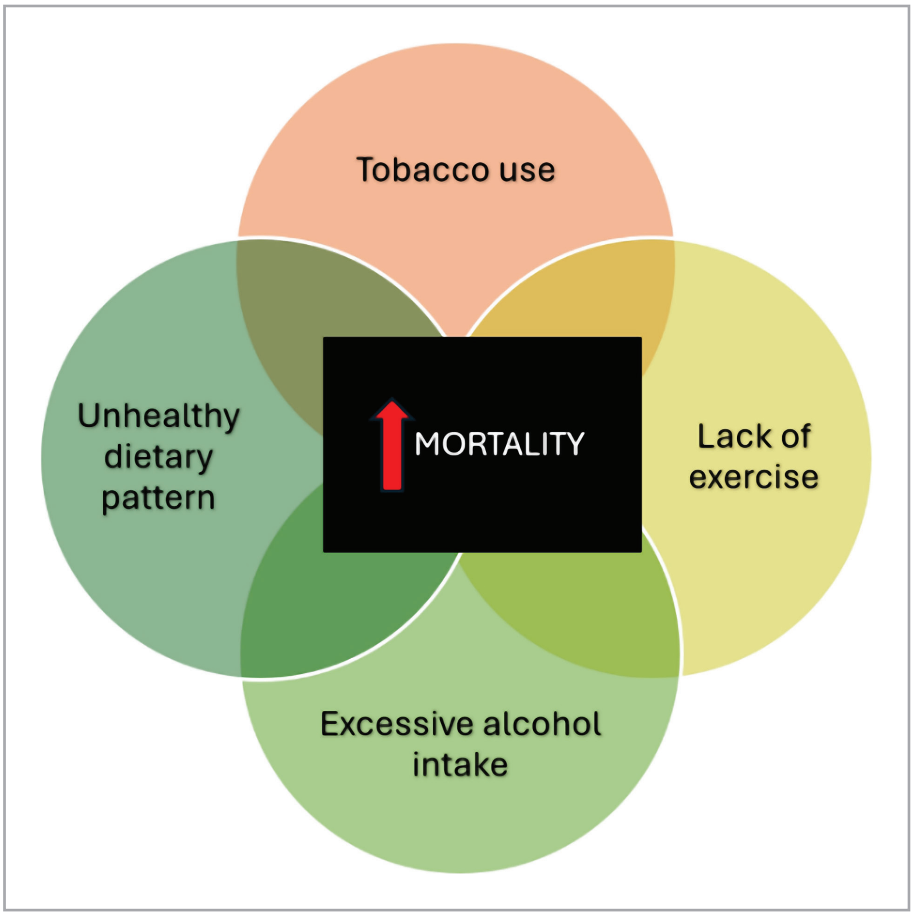

Figure 1: Risk factors linked to mortality from noncommunicable diseases.

sleep apnea, osteoarthritis, and various types of cancers [3]. More than 1.2 million deaths are caused by excessive adiposity across Europe every year [1].

Adipose tissue

Adipose tissue, commonly known as body fat, is a specialized connective tissue that stores energy as triglycerides. However, other cells contribute to its growth, *e.g.*, preadipocytes, macrophages, endothelial cells, fibroblasts, and leukocytes. Adipose tissue is distributed throughout the body, mostly found subcutaneously and in visceral depots surrounding internal organs. It plays a crucial role in regulating energy metabolism and maintaining homeostasis by storing excess energy and releasing fatty acids during periods of energy deficit. Fat cells release various hormones and signaling molecules, known as adipokines, that regulate appetite, insulin sensitivity, and inflammation. Obesity alters the structure of adipose tissue, leading to the accumulation of macrophages and excessive extracellular matrix production. This state of chronic inflammation is related to obesity-related metabolic dysfunction. Most adipokines that stimulate inflammatory responses are upregulated in obesity and, therefore, promote metabolic dysfunction [4].

Adipokines

Adipokines are cytokines secreted by adipose tissue. These include proinflammatory adipokines like leptin, tumor necrosis factor-alpha (TNFα), and interleukin-6 (IL-6), as well as anti-inflammatory adipokines such as adiponectin. Maintaining a balance between pro- and anti-inflammatory adipokines is crucial for metabolic homeostasis, as disruptions can lead to metabolic disorders such as obesity, type 2 diabetes, and cardiovascular disease. Obesity leads to a shift in the secretion of adipokines towards a more steatogenic, inflammatory, and fibrogenic profile (Figure 2). Numerous adipokines, such as visfatin, apelin, hepcidin, omentin, chemerin, and plasminogen activator protein, have been described [5], but their function surpasses the scope of this review.

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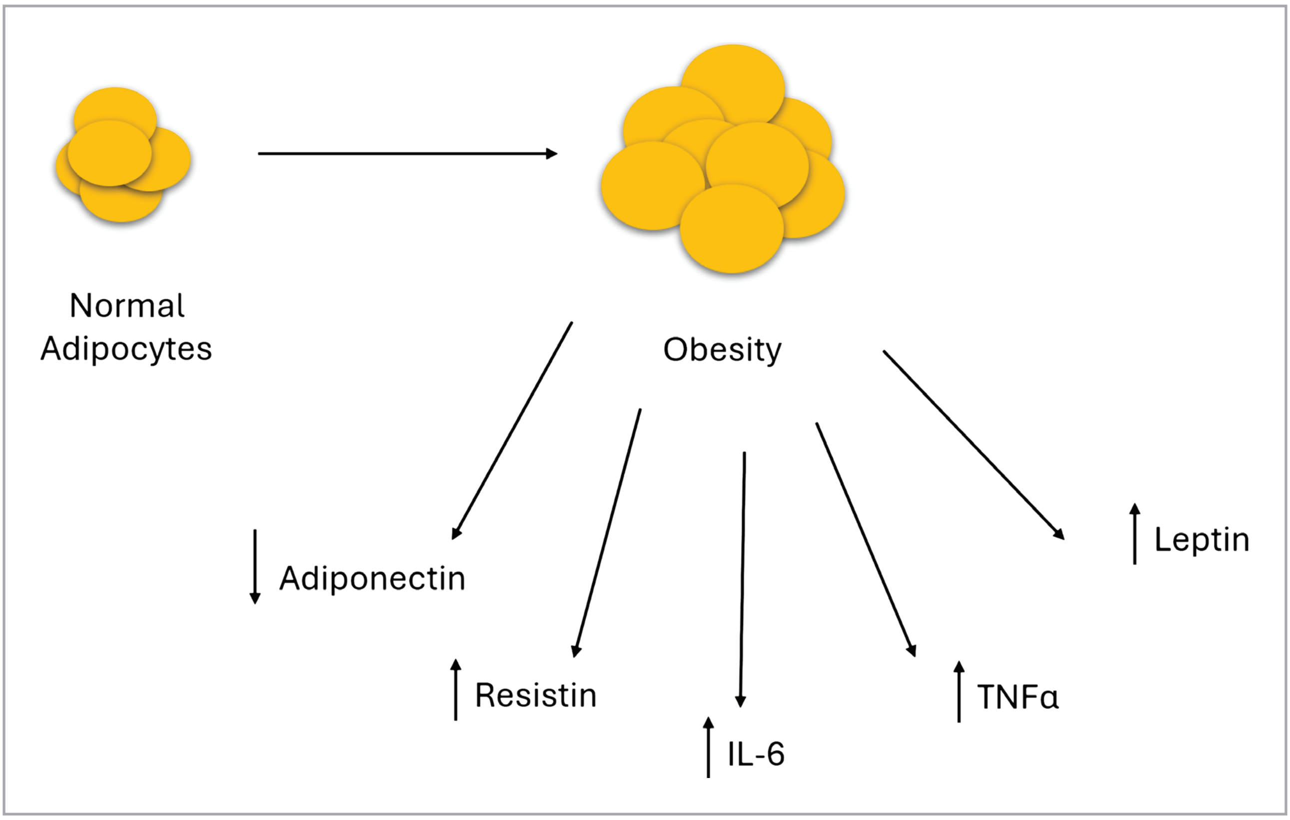

Figure 2: Changes of adipokines in obesity.

Leptin plays a vital role in regulating energy balance and appetite. It binds to receptors in the hypothalamus—a brain region responsible for hunger and satiety—suppressing food intake and enhancing energy expenditure. As a result, leptin functions as a potent anorexigenic peptide. When the body's fat stores are high, leptin levels increase and signal to the brain that sufficient energy is available. This suppresses appetite and increases energy expenditure, which helps to maintain a stable body weight and *vice versa*. However, when leptin resistance develops, as can happen in obesity, the effect of appetite suppression does not occur. It also regulates pancreatic Langerhans cells, growth hormone levels, the immune and gastrointestinal system, hematopoiesis, angiogenesis, wound healing, and bone metabolism. Inflammatory cytokines induce leptin production [5].

Resistin is a peptide secreted by adipose tissue, mononuclear cells, muscle cells, and pancreatic cells. It plays an important role in insulin resistance and glucose metabolism. Resistin is a proinflammatory molecule that stimulates inflammatory cytokines and adhesion molecules via a nuclear factor kappa B (NF-κB)-dependent pathway. Its circulating levels are elevated in obesity [6].

The most important proinflammatory cytokines related to obesity are tumor necrosis factor-alpha (TNF) and interleukin 6. Monocytes and macrophages mainly produce TNF, while adipose tissue produces one-third of the total IL-6. Both are increased in obese patients [4].

On the other hand, adiponectin is an anti-inflammatory molecule that inhibits NFκB-dependent cytokine release. In obesity, increased production of inflammatory cytokines leads to a decline in adiponectin levels [6]. Adipokine has antioxidant properties. It enhances the production of nitric oxide by endothelial cells, which helps to protect the vasculature by reducing platelet aggregation and promoting vasodilatation. Adiponectin inhibits macrophage activation and reduces foam cell accumulation, which has antiatherosclerotic effects. It also induces the expression of endothelial adhesion molecules [5].

The endocannabinoid system also regulates body weight and food intake. Both subcutaneous and visceral adipose tissue express endocannabinoid receptor type 1. Their activation results in adipogenesis and lipogenesis, leading to visceral obesity. The use of an endocannabinoid receptor type 1 antagonist suppresses appetite and food intake, resulting in weight loss [7].

The microbiota-gut-brain axis

The microbiota-gut-brain axis is the complex communication pathway between the microbes inside our digestive system, the gut, and the brain. The gastrointestinal system is regulated by intrinsic enteric neurons and glia within the enteric nervous system, as well as extrinsic fibers from the central and autonomic nervous systems. Additionally, factors outside the enteric nervous system—including the brain, other branches of the autonomic nervous system, the gut-associated immune system, and the gut microbiome—play a crucial role in influencing gastrointestinal motility. The gut communicates with these systems through complex pathways, functioning as bidirectional conduits for homeostasis, with changes in this communication associated with the disease. Maintaining proper gut function is critical for survival and brain-gut homeostasis, but the mechanisms of gut-brain communication are still being investigated [8]. The gut microbiota, a vast community of trillions of microorganisms residing in the gastrointestinal tract, plays a vital role in digestion, immune function, and various physiological processes. Emerging research reveals its significant impact on brain function and behavior, mediated through multiple pathways, including neurotransmitter production, immune signaling, and the enteric nervous system. Various neuropeptides, cytokines, and gut hormones play a complex role in the dynamic system of the microbiota-gut-brain axis [9]. Therefore, in obesity, a dysregulation of the microbiota-gut-brain axis is observed. Accumulated adipose tissue alters the autonomic nervous system, while chronic low-grade inflammation has been linked to dysbiotic microbiota and impaired immune response. In addition, high levels of circulating short-chain fatty acids can impair the functioning of microglia, the specialized immune cells in the central nervous system, which play a crucial role in the brain's innate immune system [10]. Short-chain fatty acids, produced by the gut microbiota, stimulate anorexigenic factors that prolong the feeling of satiety. Those are glucagon-like peptide one (GLP-1) and peptide YY (PYY). Decreased levels of glucagon-like peptide 1 and peptide YY in obesity are observed [11].

Obesity and digestive diseases

A broad spectrum of digestive diseases can be provoked or aggravated by overly accumulated adipose tissue in obese patients, including gastroesophageal reflux disease (GERD), inflammatory bowel disease (IBD), non-alcoholic fatty liver disease (NAFLD), gallbladder stones, pancreatitis, and various types of cancers such as bile duct, liver, pancreatic, colorectal, and esophageal cancer (Figure 3). The mechanisms underlying the relationship between obesity and digestive diseases are complex and not fully understood. However, it is hypothesized that the chronic low-grade inflammation that is characteristic of obesity may contribute to the development of these diseases. Additionally, alterations in the gut microbiota, hormonal imbalances, and changes in intestinal motility may play a role. The prevention and management of obesity may, therefore, significantly impact the reduction of the incidence and severity of these digestive diseases. In this review, a thorough analysis of the relationship between obesity and digestive diseases is presented with an up-to-date literature research done by PubMed and Google Scholar search engines.

Esophageal diseases

Gastroesophageal reflux disease (GERD) is a chronic disorder characterized by the retrograde flow of stomach contents into the esophagus, resulting in symptoms such as heartburn, regurgitation, and dysphagia. The underlying pathophysiology of GERD is multifactorial and involves dysfunction of the lower esophageal sphincter (LES), impaired esophageal clearance, and delayed gastric emptying. Obesity, hiatal hernia, pregnancy, and smoking are among the most recognized risk factors for GERD. Diagnosis of GERD is primarily based on clinical symptoms, although various tests, including endoscopy, ambulatory pH monitoring, and esophageal manometry, may be utilized to confirm the diagnosis and evaluate the severity of the disease. Treatment of GERD typically involves lifestyle modifications, such as weight loss and dietary changes, as well as pharmacological interventions, such as proton pump inhibitors and histamine receptor antagonists [12]. GERD can be classified into three main clinical categories: nonerosive reflux disease, erosive esophagitis (EE), and Barrett's esophagus (BE) [13]. Esophageal adenocarcinoma (EAC) is a malignant neoplasm originating from glandular cells in the distal esophagus. Only 10% of esophageal cancers are adenocarcinomas (EAC), but the incidence has increased more than sixfold in the last decades [14]. The main risk factors for EAC include GERD, Barrett's esophagus, obesity, and smoking [15].

Obesity is a well-known risk factor for GERD, with studies showing a positive correlation between body

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Figure 3: Impact of obesity on digestive diseases.

mass index (BMI) and the development of GERD [16–18]. The mechanism underlying this association is considered multifactorial, with several potential factors including increased intra-abdominal pressure, alterations in the hormonal milieu, and impaired function of the lower esophageal sphincter. Increased intra-abdominal pressure resulting from abdominal adiposity can contribute to developing GERD by promoting the reflux of stomach contents into the esophagus. Additionally, obesity is associated with other comorbid conditions, such as hiatal hernia, which is also a known risk factor for GERD. Consuming high-fat food, which is usually seen in obese patients, can worsen GERD symptoms, as shown by a cross-sectional study by El-Serag *et al.* [19]. High-carbohydrate diets can also contribute to the development of GERD. When carbohydrates are not fully digested and absorbed in the small intestine, they reach the colon, where they are metabolized into short-chain fatty acids and hydrogen by microflora. These short-chain fatty acids can relax the proximal stomach and trigger transient lower esophageal sphincter relaxations, leading to GERD symptoms [20]. Moreover, obesity was demonstrated to be a contributing factor in erosive esophagitis but not in Barrett's esophagus [21]. The increase in weight has been linked to the development of new erosive esophagitis lesions and the persistence of preexisting lesions diagnosed by endoscopy [22].

Barrett's esophagus can progress to esophageal adenocarcinoma (EAC) in a small portion, approximately 0,5% per year [23]. Recurrent GERD symptoms increase the risk of esophageal adenocarcinoma by approximately 8-fold compared to those without GERD symptoms [24]. Obesity, particularly abdominal obesity, is associated with an increased risk of esophageal inflammation (EE), metaplasia (BE), and neoplasia (EAC) [25].

In addition to the mechanical effect, abdominal obesity changes levels of inflammatory cytokines linked to Barret's esophagus and esophageal adenocarcinoma. Elevated leptin levels and insulin resistance increase the risk of EAC in patients with Barrett's esophagus, while high levels of adiponectin are inversely associated with EAC [26].

Liver diseases

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disorder characterized by the accumulation of fat in hepatocytes without significant alcohol consumption. NAFLD is increasingly prevalent worldwide, particularly in Western countries, and is associated with obesity, type 2 diabetes, and other metabolic disorders. NAFLD can range from a benign form, simple fatty liver (NAFL), to a more aggressive form, non-alcoholic steatohepatitis (NASH), characterized by inflammation, liver cell injury, and potentially progressing to cirrhosis and liver cancer. The pathogenesis of NAFLD involves multiple factors, which are individual for every NAFLD patient. These factors include specific genetic polymorphisms and epigenetic changes; dietary factors such as excessive fat and fructose intake; sedentary behavior; obesity and insulin resistance; adipokine dysregulation; lipotoxicity, endoplasmatic reticulum stress; oxidative stress; dysbiosis of the gut microbiota and endocrine disruptors [27]. The "two-hit" theory, which suggested that steatohepatitis required a second "hit" after steatosis, is now outdated. A conceptual framework for understanding the pathogenesis of NASH involves the liver's inability to handle primary metabolic energy substrates, which leads to toxic lipid accumulation. This lipid accumulation results in hepatocellular stress, injury, and death, leading to fibrogenesis and genomic instability that predisposes to cirrhosis and hepatocellular carcinoma. Excess fatty acid supply or impaired disposal leads to lipotoxicity, endoplasmic reticulum stress, and hepatocellular injury [28].

Obesity contributes to both the development and progression of NAFLD. It causes hepatocytes to accumulate excess lipids, primarily in the form of triglycerides, leading to lipotoxicity and glucotoxicity. Consequently, cellular stress responses are triggered, including endoplasmic reticulum stress, mitochondrial dysfunction, and oxidative stress. If left unmanaged, these stressors can lead to the progression of NAFL to NASH. Inadequate management of obesity during the simple steatosis stage can trigger an intra-hepatic inflammatory process that activates hepatic innate immune cells and progressively recruits immune cells into the liver, leading to cytokine release and inflammation. Inflammation intensifies and contributes to the fibrotic process, which arises when the inflammation persists. Immune cells interact with wound-healing cells during fibrogenesis within the liver, leading to cirrhosis and neoplasia if the counterregulatory mechanism against liver injury fails [27]. Around 23% of patients with simple non-alcoholic steatosis would progress to steatohepatitis [29].

Obesity also affects the liver through adipokines and other cytokines. They can have both positive and negative effects on the liver. For example, adiponectin can be beneficial, while TNF-α, IL-6 and resistin can be harmful. However, the effects of adipokines can be unpredictable, as they may vary depending on the stage of NAFLD. Leptin, for instance, may have antisteatotic effects in the early stages of the disease but may promote inflammation and fibrosis as the disease progresses. Similarly, adiponectin can reduce inflammation and oxidative stress in the liver, but its effects may be reversed in cirrhosis [27].

Changes in the gut microbiome affect liver homeostasis when excessive harmful compounds enter the liver via the portal circulation, resulting in increased gut permeability and endotoxemia [30]. Dysbiosis of the gut microbiota has been described in patients with cirrhosis. The gut microbiome bacteria can metabolize bile acids and nutrients, potentially altering gut-liver signaling and promoting inflammation or fibrosis [31].

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It typically arises in the context of chronic liver disease, with chronic hepatitis B and C, alcohol abuse, and NAFLD being the most common underlying conditions [32]. The incidence of HCC is higher in obese individuals, and NAFLD accounts for a substantial proportion of HCC cases. A meta-analysis of 11 cohort studies revealed that overweight and obese individuals had a 17% and 89% increased risk of developing liver cancer, respectively, when compared

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to those with normal weight [33]. Patients with NASH-related HCC may develop the condition even without cirrhosis [34]. Obese NAFLD patients are often asymptomatic but at risk for diabetes and HCC. They should be monitored regularly, using ultrasound of the liver or transient elastography if available; laboratory tests like alpha-fetoprotein, blood, and platelet counts; liver biochemical tests and prothrombin time; and cardiovascular risk screening. Treatment should focus on weight loss, exercise, diet, and lifestyle changes [35].

Pancreatic and biliary tract diseases

Gallstones are a common medical condition characterized by the formation of concretions within the gallbladder or bile ducts. They can be classified as cholesterol and pigment stones. Although most individuals with gallstones are asymptomatic, some may experience biliary colic, cholecystitis, or other complications, such as pancreatitis, cholangitis, or gallbladder cancer. The development of gallstones is a multifactorial process influenced by various factors such as female gender, family history of gallstone disease, obesity, metabolic syndrome, dyslipidemia, hyperinsulinemia, and type 2 diabetes. Estrogen treatment, high cholesterol, high-carbohydrate diets, rapid weight loss, and weight cycling also increase the risk. At the same time, unsaturated fats, coffee, moderate alcohol consumption, legumes, and physical activity can reduce the risk [36]. Compared to other risk factors, women and morbidly obese patients have the highest risk of developing gallstones [37].

Obesity is a well-established risk factor for cholesterol gallstone formation and increases the likelihood of gallbladder cancer. It influences lipid and hormone metabolism, impairs gallbladder function, and promotes gallstone development. The development of gallstones is linked to impaired gallbladder function, inflammation, and the buildup of cholesterol in bile, which is more likely to occur in individuals who are obese or have hyperinsulinemia. Other factors, such as increased mucin gel secretion in the gallbladder, slow intestinal motility, and increased cholesterol absorption in the intestine, also contribute to the formation of gallstones and are closely linked to obesity and hyperinsulinemia [38].

The role of obesity in the development of cholangiocarcinoma is controversial. Most studies in Western countries report a positive correlation between obesity and cholangiocarcinoma and a null effect in the Asian population. This difference may be explained by the different prevalence of obesity in Asian and Western countries, as well as the pathophysiology of the disease, race, and genetic variation [39].

Obesity is also a risk factor for acute pancreatitis regardless of the etiology (gallstones, alcohol, others, or unknown causes). It can be used as a prognostic factor in patients with acute pancreatitis, where obese patients had a significantly increased risk of severe course of the disease, local and systemic complications, and in-hospital mortality compared with non-obese patients [40].

Pancreatic cancer, one of the deadliest cancers in adults, has a limited number of established risk factors that can explain only a tiny proportion of cases, including smoking, diabetes, heavy alcohol consumption, family history, increasing age, and rare inherited genetic conditions like Peutz-Jeghers, familial melanoma, and hereditary pancreatitis [41]. However, obesity is a significant risk factor for pancreatic cancer and is associated with worse prognosis and decreased overall survival compared to non-obese patients. The exact mechanisms underlying this relationship are poorly understood and likely involve multiple factors, including the effects of adipose tissue on insulin, hormones, cytokines, and environmental exposure to carcinogens [42].

Colorectal adenoma and cancer

Colorectal adenoma and cancer are neoplastic lesions that arise from epithelial cells of the large intestine. Colorectal cancer is the malignant alteration of conventional adenomas and sessile serrated polyps or adenomas. The adenoma-carcinoma sequence is the most widely accepted model for colorectal carcinogenesis, and it suggests that the progressive accumulation of genetic and epigenetic alterations leads to the development of cancer. Therefore, the prevalence of adenomas has been studied extensively, and screening methods such as colonoscopy have identified adenomas in up to 50% of asymptomatic individuals. Among these adenomas, 3.4% to 7.6% are advanced, and 0.2% to 0.6% are cancerous [43].

Obesity is a well-established risk factor for colorectal adenoma and cancer. Recent studies suggest that abdominal obesity and metabolic syndrome may be stronger predictors of colorectal carcinoma than BMI [44]. A consistent association between BMI and a higher risk of colon or rectal cancer in men is acknowledged, but this association is weaker in women. This gender difference could be due to variations in the prevalence and onset age of metabolic syndrome or a protective effect of estrogen that induces apoptosis and inhibits cell proliferation. Additionally, there are suggestions that obesity may decrease the overall survival of patients with colorectal carcinoma, irrespective of metabolic syndrome, with potential gender-specific variations [45].

Inflammatory bowel diseases

Inflammatory bowel diseases (IBDs) are chronic disorders that cause inflammation in the gastrointestinal tract. IBD has a strong genetic component, but recent studies have revealed that environmental factors play a critical role in the pathogenesis of Crohn's disease and ulcerative colitis. Environmental triggers, such as diet, medications, and smoking, influence the changes in the microbiome. Such changes will compromise the intestinal barrier and increase gut permeability, leading to continuing inflammation, a dysregulated immune system, and the appearance of symptoms.

While it is commonly believed that patients with inflammatory bowel disease are malnourished and underweight, research suggests that a significant proportion of the IBD population, ranging from 15% to 40%, is obese [46]. Patients with Crohn's disease exhibit a localized form of visceral adipose tissue called creeping fat, limited to areas of inflamed bowel, which is more immunologically active than other adipose tissue. Levels of adipokines such as leptin and resistin are increased in such patients and can correlate with the severity and activity of the disease. Both obesity and inflammatory bowel disease exhibit gut microbiota dysbiosis and a compromised intestinal barrier. Visceral obesity could, therefore, promote intestinal inflammation and contribute to the development and progression of Crohn's disease [47]. However, epidemiological data about the association between obesity and IBD are conflicting, and some even show a protective effect [46, 48].

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder characterized by recurrent abdominal pain, bloating, and changes in bowel habits, such as constipation, diarrhea, or a combination of both. The exact cause of IBS is still unclear, but it is thought to result from a combination of factors. Individuals with a genetic predisposition and susceptible microbiome may experience the onset of IBS in the gut, possibly caused by infections or exposure to environmental antigens, such as specific foods, which can alter the microbiome, increase intestinal permeability, and ultimately result in gut hypersensitivity, motor abnormalities, inflammation, and other non-gastrointestinal symptoms. Additionally, primary abnormalities of the stress pathway, abnormal bile acid metabolism, establishment of a methanogenic flora after infection, and learned behavioral responses leading to pelvic floor dysfunction can also contribute to the development of IBS [49].

The relationship between IBS and diet is complex and multifactorial. Although genetics were once thought to be a major factor, current research suggests that environmental influences, particularly diet, significantly impact the composition of gut bacteria. In the symbiotic host/bacteria relationship, gut bacteria rely on the host's consumption of complex polysaccharides to promote growth, and humans, in turn, rely on gut bacteria to break down complex nutrients. Foods play an essential role in triggering symptoms of IBS, and several mechanisms, such as the osmotic effect of short-chain carbohydrates and alterations in gut microbiota and bacterial fermentation, have been proposed [50]. Although the incidence of obesity and irritable bowel syndrome is increasing, they share some specific pathophysiological mechanisms, such as shifts in gut microbiota. The direct association between these diseases is not yet established, and future investigations are required.

Conclusion

Obesity has been shown to play a significant role in the development and progression of various benign digestive diseases, including gastroesophageal reflux disease, non-alcoholic fatty liver disease, gallstones, and pancreatitis. Individual everyday choices of diet, physical activity, tobacco and alcohol use, medications, and stress management have been recognized to influence human metabolism and homeostasis profoundly. Changes in gut microbiota and increased intestinal permeability result in immune system dysregulation. Adipose tissue and adipokines contribute to a proinflammatory state in the digestive system, leading to chronic inflammation and tissue damage. Altogether, these accumulated changes can promote the development of

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malignant diseases such as hepatocellular carcinoma, colorectal cancer, and esophageal adenocarcinoma. Weight management and lifestyle modifications are essential in preventing and managing obesity-related digestive diseases.

Conflict of interest

The authors declare no conflict of interest.

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