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Interplay Between Metabolic Syndrome and Gastrointestinal Disorders: Pathophysiology and Clinical Implications

Lakshmi Chandini M*, Bhavana U and Vaishnavi P

Omega College of Pharmacy, India

***Corresponding authors:** Lakshmi Chandini Mandepudi, Omega College of Pharmacy, Edulabad, Hyderabad, Telangana, India, Email: chandinimandepudi72@gmail.com

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Abstract

The term "metabolic syndrome" refers to a collection of metabolic disorders, the most common of which is obesity, particularly abdominal obesity. Many chronic diseases, including cardiovascular disease, have metabolic syndrome as a risk factor. Furthermore, the rise in obesity-related disorders linked to a poor lifestyle that include dyslipidaemia, hypertension, and irregularities in glucose metabolism—a condition known as metabolic syndrome (MS)—has been problematic. In addition to being linked to digestive system issues, such as upper gastrointestinal diseases, MS has also been found to be a risk factor for arteriosclerotic diseases and ischemic heart disease. Multiple gastrointestinal disorders, including colorectal cancer and gastroesophageal reflux disease, have been associated with obesity. Obesity as manifested by an elevated body mass index is not as significant as abdominal obesity as a contributing factor to the development of these diseases, according to recent research. Apart from the physiological consequences of obesity, such as elevated intra-abdominal pressure due to substantial adipose tissue, substances secreted by adipose tissue, including insulin-like growth factor-1, interleukin-6, leptin, and tumour necrosis factor-α, have been suggested as pathogenic mediators of these disorders. Unlike high body weight and high body mass index, visceral fat accumulation associated with abdominal obesity is linked to the onset of several diseases of the digestive system because it can raise intra-abdominal pressure, which triggers the release of several bioactive substances known as adipocytokines, such as tumour necrosis factor-a, interleukin-6, resistin, leptin, and adiponectin. This review article focuses on obesity, visceral fat build-up, and the main upper gastrointestinal ailments, as well as their correlation with multiple sclerosis. Within this review, we discuss the relationship between digestive disorders and metabolic syndrome or its component parts, with a particular emphasis on obesity and abdominal obesity.

Keywords: Metabolic Syndrome; Gastrointestinal Disorders; Pathophysiology; Clinical Implications; Abdominal Obesity

Key Insights

- Abdominal obesity is a more significant risk factor for gastrointestinal diseases than general obesity, with adipose tissue secretions like tumor necrosis factor-alpha and interleukin-6 playing pathogenic roles.
- Gut dysbiosis contributes to the pathogenesis of both gastrointestinal disorders and metabolic syndrome, with bioactive dietary components such as fibers and polyphenols potentially serving as alternative treatments by restoring normal intestinal flora.
- The gastrointestinal tract is integral to metabolic syndrome, with bariatric surgery being an effective treatment for obesity-related type 2 diabetes due to

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changes in gut hormones and microbiota.

- Traditional Chinese medicine may treat metabolic syndrome-related diseases like diabetes and NAFLD by influencing the composition and metabolism of intestinal microorganisms.
- Metabolic syndrome components, particularly abdominal obesity and insulin resistance, are implicated in the development of colorectal cancer.
- NAFLD, the major hepatic disorder in metabolic syndrome patients, is influenced by insulin resistance, abnormal lipid metabolism, and dysregulation of cytokines/adipokines.
- The gut microbiome has a substantial influence on metabolic syndrome risk factors, with a defective gut barrier and microbially produced metabolites affecting host metabolism.
- Metabolic and bariatric surgeries address the metabolic syndrome by altering neurohormonal mechanisms, which can lead to the resolution of clinical and biochemical manifestations.
- Metabolic syndrome is associated with an increased risk of gastrointestinal cancers, with central obesity being a core driver of this risk.
- Metabolic syndrome and inflammatory bowel disease share pathophysiological features such as adipose tissue dysregulation and chronic inflammation, suggesting potential common therapeutic targets.

Abbreviations

MS: Metabolic Syndrome; HDL: High-Density Lipoprotein; ATP: Adult Treatment Panel; IDF: International Diabetes Federation; WHR: Waist-to-hip Ratio; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; GERD: Gastroesophageal Reflux Disease; BE: Barrett's Oesophagus; LES: Lower Oesophageal Sphincter.

Introduction

The term metabolic syndrome (MS) refers to the build-up of visceral fat together with disorders linked to a certain lifestyle that include dyslipidaemia, hypertension, and irregularities in glucose metabolism [1]. A cluster of metabolic abnormalities, metabolic syndrome is defined as having three or more of the following characteristics: high blood pressure, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides, elevated abdominal obesity (increased waist circumference [WC), and high fasting glucose.

Cardiovascular and other chronic disease are at risk due to metabolic syndrome. Worldwide use has been made of the MS diagnostic criteria that the Adult Treatment Panel (ATP) III and the International Diabetes Federation (IDF) accepted, although Japan frequently uses the MS criteria that a joint committee of eight Japanese medical societies established in 2005.The metabolic syndrome is receiving more and more attention, and the most clinically significant obesity pattern has been considered to be abdominal obesity, particularly visceral obesity (i.e., the build-up of intra-abdominal fat). Waist-to-hip ratio (WHR) and waist circumference (WC) are sensitive indicators of visceral obesity. While numerous research has examined the connection between obesity and various gastrointestinal disorders, there is a dearth of information regarding the potential risk factors for gastrointestinal disorders associated with metabolic syndrome or abdominal obesity [2]. We examine the relationship between gastrointestinal disorders and the metabolic syndrome, or its component parts, with a particular emphasis on obesity and abdominal obesity. Recent lifestyle changes, such as increased fat intake and decreased activity, have contributed to a rise in MS cases that has been problematic in both developed and developing nations. Insulin resistance is associated with a number of pathophysiological disorders, including altered adipocytokine production from visceral fat in MS patients. Multiple sclerosis (MS) has a significant influence on public health and medical costs since it can cause a variety of disorders, including ischemic heart disease and abnormalities of the digestive system, including upper gastrointestinal diseases. Aspirin, ibuprofen, and diclofenac are examples of non-steroidal anti-inflammatory drugs (NSAIDs); genetic predisposition to the disease; pharmaceutical therapies (i.e., antibiotics, not limited to those administered for human use but potentially including those used in farm animals and crops and ingested with the resultant foods); and unhealthy lifestyles (i.e., irregular eating, physical inactivity, smoking, and low fibre diets) are the main causes of gastrointestinal disorders [3-5]. Furthermore, Helicobacter pylori, a Gram-negative bacterial infection that may cause IBD and functional gastrointestinal diseases, affects roughly 50% of the world's population. Abdominal pain, constipation, diarrhoea, abdominal distention, stomach acidity, gastrointestinal reflux disease (GERD), bleeding in the GI tract, malnourishment or malabsorption, and intestinal blockage are frequent symptoms of all GI illnesses [6,7]. Currently, laxatives, anti-diarrheal, opioids, anti-emetics, motility enhancers, anti-acidity, anti-ulcer, and anti-inflammatory agents are some of the medications used to treat GI issues. Traditional treatments for inflammatory bowel disease (IBD) use corticosteroids, immunosuppressant's, and anti-tumor necrosis factor (TNF)-α antibodies. These treatments are frequently associated with an increased risk of opportunistic infections and dysplasia's, which can have costly effects on the management of the health system [8,9]. Research points to the Western pattern diet (WPD) as the cause of the widespread occurrence of GERD. According to studies, GERD is more common in North America (18.1–27.8%), Europe

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(8.8–25.9%), Australia (11.6%), South America (23%), East Asia (2.5–7.8%), and the Middle East (8.7–33.1%). Though the prevalence of dyspepsia varies from nation to nation, Ford et al. indicate a 21% pooled prevalence [10,11]. Diarrhoea causes more than 128,000 hospital admissions and 3000 fatalities in the adult population in the United States. Likewise, extant research indicates that 12% of the global populace has experienced constipation.

The etiopathogenesis of GI illnesses remains unclear, and there is currently no marker that can definitively diagnose them, despite recent advancements in our understanding of the pathophysiological pathways involved [12,13]. Several known etiological variables include infections, genetic and epigenetic modifications, stress, gut microbiota alterations that result in dysbiosis, and visceral hypersensitivity.

When discussing the function of insulin resistance in human disease, Reaven (1988) emphasised the clinical significance of multiple sclerosis [14,15]. Numerous metabolic disorders, such as gout, hypertension, and hyperglycaemia, were already documented in the 1920s, according to Sadeghi. Later, in 1947, Vague identified metabolic problems, cardiovascular disease, and type 2 diabetic mellitus (T2DM) as factors influencing the obese phenotype. Insulin resistance and glucose intolerance are recognised as critical elements of multiple sclerosis (MS) in both the European Group for the Study of Insulin Resistance and the WHO classification. The past 20 years have seen a significant rise in the global MS population, which has been linked to an epidemic of obesity and type 2 diabetes [16-18]. Approximately 20–25% of adults worldwide have multiple sclerosis. According to WHO estimates, 422 million people have diabetes, 1.13 billion have hypertension, and 650 million have obesity. These days, it is understood that nutrition and lifestyle choices are essential to preventing diseases including MS, T2DM, cardiovascular disease, and gastrointestinal issues [19,20]. Moreover, the most recent research indicates that the balance of gut microbiota is restored by modulating intestinal dysbiosis with dietary supplements. The goal of this review is to provide an overview of the current understanding of the protective roles of functional dietary components in both GI and MS, taking into account that dysbiosis may be a common link between GI disorders and MS and that the restoration of altered microbiota through diet is thought to be the first line of treatment for both conditions [21,22].

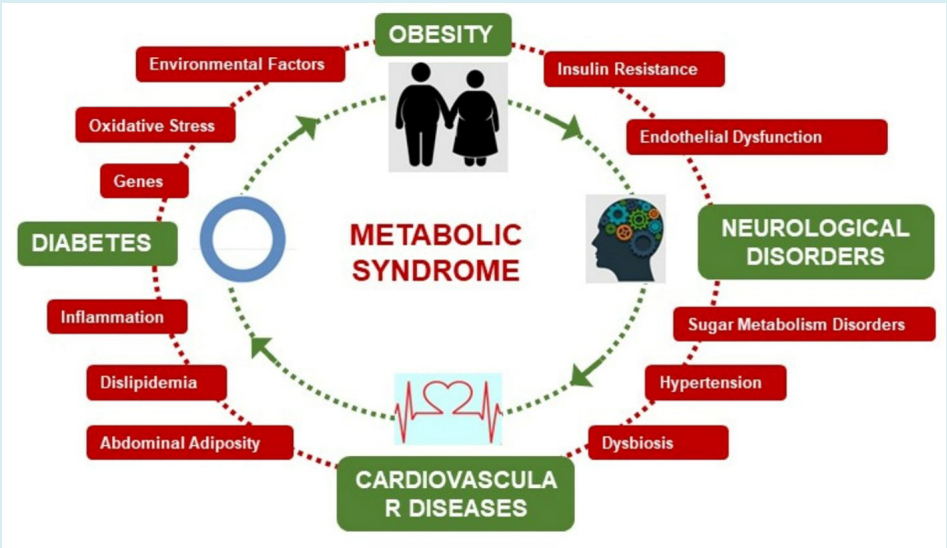

Figure 1: Metabolic Syndrome Causing Different Diseases.

Hiatal Hernias

Hiatal hernias are a common condition that can mimic other diseases and have significant implications for upper gastrointestinal health. They are particularly relevant in the context of gastroesophageal reflux disease (GERD) and can be associated with other conditions such as metabolic syndrome [23]. Hiatal hernias can mimic symptoms of cardiovascular and gastrointestinal diseases, leading to substernal and upper abdominal complaints, and are often associated with conditions like angina pectoris and peptic ulcer. The size of a hiatal hernia is directly related to the severity of lower oesophageal sphincter (LES) dysfunction, oesophageal acid exposure, and mucosal injury in GERD patients [24]. Larger hernias result in weaker LES, increased acid reflux, and more severe esophagitis. Hiatal hernias can have clinical implications beyond GERD, such as in patients with right isomerism, where they are associated with symptoms like vomiting and recurrent airway infections, and may have a potential link to sudden death [25].

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Cameron ulcers, which are linear gastric ulcers found in large hiatal hernias, can cause severe upper gastrointestinal haemorrhage. Treatment options for Cameron ulcers include high-dose proton pump inhibitors or surgery, depending on individual patient circumstances [26].

In conclusion, hiatal hernias play a significant role in upper gastrointestinal diseases, affecting LES function and contributing to conditions like GERD and Cameron ulcers. The size of the hernia is a critical factor in the severity of associated symptoms and mucosal damage [27]. Additionally, hiatal hernias can have broader clinical implications, particularly in patients with specific anatomical anomalies such as right isomerism. Treatment approaches vary and should be tailored to the individual patient's needs [28].

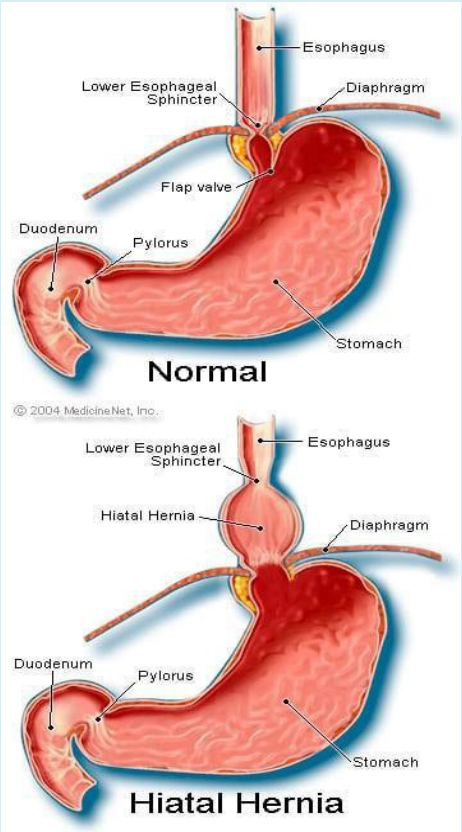

Figure 2: Hiral Hernia.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a prevalent condition that negatively impacts the quality of life and has been increasingly associated with metabolic syndrome (MS). The relationship between MS and GERD, including its complications such as Barrett's oesophagus (BE), has been the subject of various studies, revealing a complex interplay between these conditions [29].

Metabolic syndrome is significantly associated with a higher prevalence of GERD, as evidenced by systematic reviews and cross-sectional studies, suggesting MS as an independent risk factor for GERD [30]. The presence of MS components, particularly central obesity and abnormal fasting glucose levels, has been independently linked to GERD, indicating that central obesity may play a more critical role than BMI alone in this association [31]. Metabolic syndrome has been identified as a risk factor for the development of Barrett's oesophagus, independent of reflux symptoms, suggesting a potential reflux-independent pathway in the pathogenesis of BE [32].

Studies have shown that metabolic syndrome is associated with both erosive esophagitis and Barrett's oesophagus, with a greater risk of concurrent MS in patients with these conditions [33]. There is no significant difference in the prevalence of central obesity and metabolic syndrome between patients with Barrett's oesophagus and those with GERD, indicating that these factors may not directly influence the development of BE in a reflux population [34]. Decreased levels of adiponectin in obese patients with GERD have been observed, which may indicate a relationship between GERD and metabolic syndrome.

The synthesis of the research indicates a strong association between metabolic syndrome and gastroesophageal reflux disease [35]. Metabolic syndrome, particularly factors like central obesity and abnormal glucose levels, appears to be an independent risk factor for GERD and its complications, including Barrett's oesophagus [36]. This relationship suggests that the management of metabolic syndrome may play a role in the treatment and prevention of GERD and its progression [37].

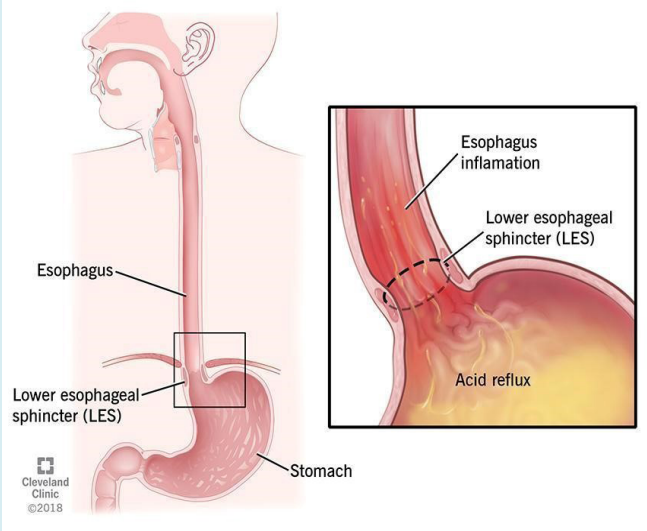

Figure 3: Showing Gastroesophageal Reflux Disease.

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Barrett's Oesophagus

Barrett's oesophagus (BE) is a condition that can arise as a complication of gastroesophageal reflux disease (GERD), and it is characterized by the replacement of the normal squamous epithelium of the oesophagus with columnar epithelium. Metabolic syndrome is associated with an increased risk of Barrett's oesophagus, particularly in patients without symptomatic reflux, suggesting a potential GERD-independent inflammatory pathway for BE pathogenesis [38].

Central obesity and metabolic syndrome are prevalent in patients with Barrett's oesophagus, with a significant association between the length of specialized intestinal metaplasia and the presence of metabolic syndrome. The prevalence of metabolic syndrome in patients with Barrett's oesophagus exceeds population norms, and metabolic syndrome is associated with elevated levels of proinflammatory markers such as C-reactive protein and interleukin-6 [39]. There is no significant difference in the prevalence of central obesity and metabolic syndrome between Barrett's oesophagus and gastroesophageal reflux disease patients, indicating that these factors may not impact the development of BE in a reflux population. Metabolic syndrome is associated with Barrett's oesophagus independent of other risk factors such as smoking, alcohol consumption, and body mass index, and this association remains robust in various analyses. The systemic inflammatory state induced by metabolic syndrome may represent a reflux-independent inflammatory pathway that increases the risk of Barrett's oesophagus, but it does not appear to increase the risk of oesophageal adenocarcinoma in the studied population [40].

The research indicates a strong association between metabolic syndrome and the risk of developing Barrett's oesophagus, especially in the absence of gastroesophageal reflux symptoms. Central obesity and metabolic syndrome are common in BE patients and are linked to a proinflammatory state [41]. However, the presence of metabolic syndrome does not significantly differ between BE and GERD patients, suggesting that while MS may contribute to the risk of BE, it does not necessarily differentiate between BE and GERD in terms of disease progression. The findings underscore the importance of considering metabolic syndrome as a potential independent risk factor for Barrett's oesophagus, separate from the effects of gastroesophageal reflux [42].

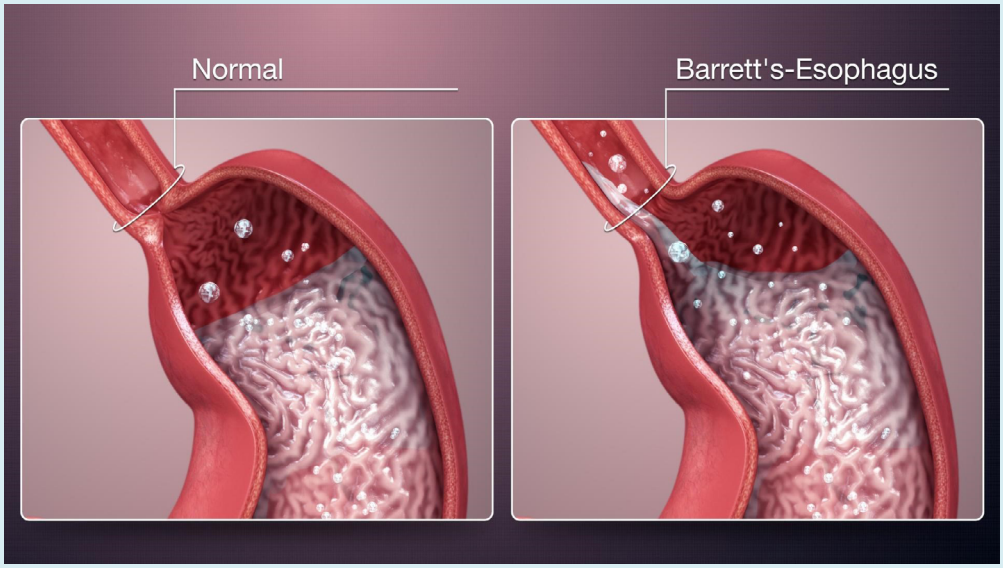

Figure 4: Barrett's Esophagus Explained Shown Using Medical Animation Still Shot.

Esophageal Adenocarcinoma

Oesophageal adenocarcinoma (EA) is a type of cancer that arises from the oesophagus, often associated with Barrett's oesophagus and influenced by various risk factors, including metabolic syndrome (MS).

Adenocarcinomas of the oesophagus and stomach show differential activity in functional modules related to inflammation and lipid metabolism, with lipid metabolism being active in intestinal metaplasia and inactive in adenocarcinomas [43]. A significant proportion of patients with Barrett's oesophagus exhibit metabolic syndrome

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and central adiposity, with a higher prevalence in those with longer segments of specialized intestinal metaplasia. Metabolic syndrome is associated with an increased risk of gastric adenocarcinoma, particularly in women, with high waist circumference also associated with an increased risk of oesophageal adenocarcinoma [44]. Metabolic syndrome may represent a GERD-independent inflammatory pathway that increases the risk of Barrett's oesophagus but does not appear to increase the risk of oesophageal adenocarcinoma The incidence of oesophageal adenocarcinoma has been rising, with known risk factors including GERD, obesity, and tobacco smoking, but the role of metabolic syndrome requires further investigation [45]. There is no significant difference in the prevalence of central adiposity and metabolic syndrome between patients with Barrett's oesophagus and those with GERD, suggesting that these factors may not independently affect the development of Barrett's oesophagus in a reflux population.

The research indicates a complex relationship between metabolic syndrome, Barrett's oesophagus, and oesophageal adenocarcinoma. Metabolic syndrome is linked to an increased risk of Barrett's oesophagus, particularly in the absence of GERD, and may contribute to the progression of gastrointestinal diseases through inflammation and altered lipid metabolism [46]. While central adiposity and metabolic syndrome are common in both Barrett's oesophagus and GERD, their direct impact on the development of oesophageal adenocarcinoma remains unclear, necessitating further research to understand the mechanisms and potential interventions [47].

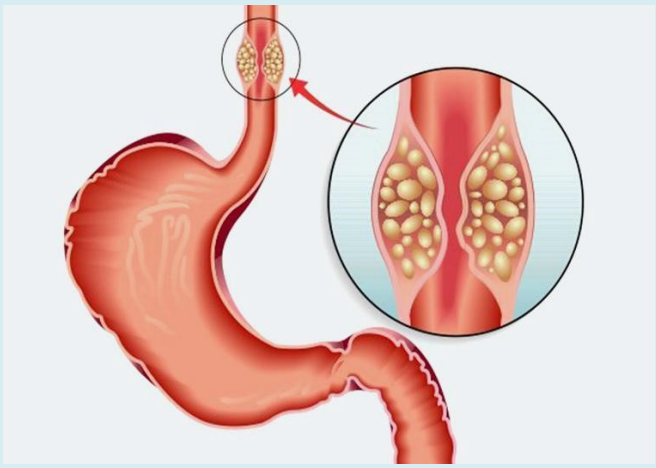

Figure 5: Esophageal (Food-Pipe) Cancer.

Gastric Adenocarcinoma

Gastric adenocarcinoma, a prevalent form of stomach cancer, has been increasingly studied in relation to metabolic syndrome, a cluster of conditions including increased waist circumference, elevated triglycerides, reduced high-density lipoprotein cholesterol, hypertension, and high glucose levels. This interest stems from the potential influence of metabolic disorders on the development and progression of gastrointestinal diseases [48]. Metabolic syndrome is significantly associated with an increased risk of gastric adenocarcinoma, particularly in women, with high waist circumference, hypertension, and high non-fasting glucose levels being notable risk factors. The presence of metabolic syndrome prior to surgery predicts a higher mortality rate for gastric cancer patient's post-gastrectomy, with hyperglycaemia being a critical factor, especially in the early stages of gastric cancer [49].

Gastric adenocarcinoma can manifest as part of a familial syndrome known as GAPPS, characterized by fundic gland polyps and a high risk of cancer confined to the proximal stomach, without association with colorectal or duodenal polyposis [50]. Metabolic syndrome components, such as higher triglyceride levels, lower HDL-C levels, and hypertension, are more prevalent in gastric cancer patients, suggesting a role in cancer development and progression, particularly in poorly differentiated and advanced-stage cancers. In contrast to gastric adenocarcinoma, metabolic syndrome does not show a significant association with oesophageal adenocarcinoma or oesophageal squamous-cell carcinoma. Abdominal obesity, rather than overall obesity, is emphasized as a more critical factor for the development of gastrointestinal diseases, including gastric adenocarcinoma.

The research indicates a strong link between metabolic syndrome and the risk of developing gastric adenocarcinoma, with specific components of the syndrome such as abdominal obesity, hypertension, and hyperglycaemia being particularly influential [51]. This association is more pronounced in women and can significantly affect mortality rates following surgical treatment for gastric cancer. Additionally, certain familial syndromes highlight the genetic predisposition to gastric adenocarcinoma, emphasizing the need for awareness and screening in affected families [52]. While metabolic syndrome is a clear risk factor for gastric adenocarcinoma, its role in other gastrointestinal cancers, such as oesophageal cancer, is less evident. Overall, these findings underscore the importance of managing metabolic disorders to potentially reduce the risk and improve outcomes for gastric adenocarcinoma patients [53].

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Obesity and GI Disorders	Insulin Resistance and GI Disorders	Dyslipidaemia and GI Disorders	Hypertension and GI Disorders	Hyperglycaemia and GI Disorders
Gastroesophageal Reflux Disease (GERD): Obesity increases the pressure in the abdominal cavity, which can lead to the development of GERD. Excess body fat, especially around the abdomen, can push the stomach upward and cause acid to reflux into the oesophagus.	**NAFLD**: Insulin resistance is closely linked to the development of NAFLD. It promotes the accumulation of fat in the liver and contributes to inflammation and fibrosis.	**Gallstones:** High levels of triglycerides and low levels of high-density lipoprotein (HDL) cholesterol are associated with an increased risk of gallstones. Gallstones can block the bile ducts, causing pain, infection, and jaundice.	**Ischemic Colitis:** Hypertension can contribute to ischemic colitis, where reduced blood flow to the colon causes inflammation and injury.	**Gastroparesis:** Chronic high blood sugar levels can damage the nerves that control the stomach muscles, leading to gastroparesis. This condition slows or stops the movement of food from the stomach to the small intestine.
Non-alcoholic Fatty Liver Disease (NAFLD): Obesity is a major risk factor for NAFLD, a condition where fat accumulates in the liver in the absence of significant alcohol consumption. This can progress to non-alcoholic steatohepatitis (NASH), cirrhosis, and liver cancer.	**Pancreatitis:** Insulin resistance and hyperglycaemia can lead to pancreatitis, an inflammation of the pancreas. Chronic pancreatitis can result in exocrine pancreatic insufficiency, where the pancreas cannot produce enough digestive enzymes.	**Atherosclerosis:** Dyslipidaemia contributes to atherosclerosis, which can affect blood vessels supplying the GI tract, potentially leading to ischemic bowel disease.	**Portal Hypertension:** High blood pressure can also lead to portal hypertension, which is high blood pressure in the portal vein that supplies the liver. This can result in complications such as varices (enlarged veins) in the oesophagus and stomach, which can bleed.	**Diabetic Enteropathy:** Hyperglycaemia can also affect the small and large intestines, leading to symptoms like diarrhoea, constipation, and abdominal pain.

Table 1: Various Metabolic Syndromes Explaining Implementation towards the GI Disorders.

Figure 6: Gastric Adenocarcinoma.

Gastroesophageal Reflux Disease, Barrett's Esophagus and Esophageal Adenocarcinom

In the United States and the Western world, obesity and gastroesophageal reflux disease (GERD) are two of the most prevalent conditions, and their rates have been rising sharply. Recent research indicates that 20% of Americans may have GERD [54]. In the US population, the prevalence of obesity (body mass index (BMI) ≥ 30 kg/m2) is 30.5%. Increases in GERD symptoms are connected with higher BMIs, and a correlation has been documented between GERD symptoms and obesity [55,56]. A BMI > 30 kg/m2 was found to be one risk factor [odds ratio (OR) 2.8; 95% confidence interval (CI), 1.7–4.5, compared with normal weight, which is defined as BMI ≤ 24 kg/m2] in a cross-sectional population-based study conducted in the United States by Lock et al. [57] to assess risk factors for the development of GERD symptoms. A cross-sectional population-based study conducted in the UK revealed an effective and positive correlation between BMI and the frequency of GERD symptoms.

In comparison to people of normal weight, the odds ratios (ORs) for the frequency of acid regurgitation and heartburn in obese individuals were 2.91 (95% CI, 2.07–4.08) and 2.23 (95% CI, 1.44–3.45), respectively. Additionally, a population-based study conducted in Germany found a substantial correlation between GERD symptoms and being overweight

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or obese [58]. However, a population-based study conducted in Sweden discovered that there was no correlation between reflux symptoms and BMI, and that the OR of recurrent GERD symptoms in adults who had ever been obese or overweight (BMI ≥ 25 kg/m2) compared to those who had never been obese or overweight was 0.99 (95% CI, 0.66–1.47) [59].

Exams with an esophagogastroduodenoscopy are not typically conducted in cross-sectional population-based investigations. Consequently, those suffering from Barrett's oesophagus (BE), oesophageal adenocarcinoma (EAC), GERD (both nonerosive and erosive), or other medical conditions are all included.

The range of diagnosis could have an impact on the outcomes. The mean BMI is substantially greater in patients with erosive GERD than in those with nonerosive GERD in studies where endoscopic examinations were conducted in patients exhibiting symptoms of GERD [60,61]. According to research by Van Oijen et al., [62] there is a tendency for obesity to be linked to both erosive GERD and GERD symptoms when examining the relationship between BMI and GERD symptoms in a group referred for upper gastrointestinal endoscopy [63]. El-Serag, et al. [64] investigated if the correlation between obesity and GERD symptoms remained after controlling for other established risk factors for GERD, such as age, sex, race, and smoking. Weekly heartburn or regurgitation was associated with to a BMI > 30 kg/m^2 (adjusted OR, 2.44; 95% CI, 1.27–4.67) as in contrast to a BMI < 25 kg/m^2. Obesity and overweight (body mass index, 25–30 kg/m^2) were both significant independent risk factors for erosive GERD. However, Lundell, et al. [65] found no correlation between abnormal acid reflux or erosive GERD and being significantly overweight (BMI, 42.5 ± 5.2 kg/m^2).

There is a sex difference in the relationship between GERD symptoms and obesity, according to [66] Nilsson et al. Higher BMI was positively associated with GERD symptoms in both sexes, but the correlation was larger in female patients. In addition, there was a difference in the strength of the connection between premenopausal and postmenopausal women. Both being overweight (BMI, 25–30 kg/m2) and obese (BMI > 30 kg/m2) were related to a statistically significant increase in the risk for GERD symptoms, with ORs of 1.43 (95% CI, 1.158–1.774) and 1.94 (95% CI, 1.468–2.566), respectively, in a recent meta-analysis [67] of published data on the association between obesity and GERD. Additionally, being overweight or obese was a risk factor for erosive GERD (OR, 1.76; 95% CI, 1.156–2.677). Both of these findings were associated to a statistically significant increase in the risk for GERD symptoms.

Empirical observations suggest that losing weight can help lessen GERD symptoms. The results of Nilsson et al. support the theory that if there is a direct correlation between obesity and GERD, weight change should affect GERD symptoms or the severity of erosive GERD. They demonstrated that, in comparison to people with stable BMI, the risk of reflux symptoms was higher (OR, 2.7; 95% CI, 2.3–3.2) in those who gained more than 3.5 BMI units, but the risk of GERD symptoms was lower (OR, 0.6; 95% CI, 0.4–0.9) in those who lost more than 3.5 BMI units. On the other hand, there is inconsistent data about the relationship between weight loss and improved GERD symptoms [68,69]; certain reports indicate a reduction in GERD symptoms, while others do not.

The contradictory findings could be explained by either irreversible abnormality at the esophagogastric junction, like a hiatal hernia, or by the weight loss being insufficient to produce an improvement after the increase in BMI [70].

The evaluation of the correlation between GERD and BMI entails a number of confounding variables. Although several statistics point to an increased incidence of GERD in overweight or obese patients, the link between obesity and GERD is still unclear. It was recently revealed that WC and BMI were related to the same level of oesophageal acid exposure. A BMI ≥ 30 kg/m2 was no longer substantially correlated with any indicators of oesophageal acid exposure after controlling for WC. Consequently, obesity as indicated by an elevated BMI may not be the primary cause of GERD symptoms [71] than abdominal obesity. To test this theory, more research is required.

Over the past three decades, squamous cell carcinoma of the oesophagus has remained steady in the United States and other Western countries, whereas the incidence of oesophageal adenocarcinoma has been progressively rising. The incidence of EAC increased significantly in white men. Sex and race variations in occurrence still exist, despite the fact that rising incidences have been observed in white women and black men: the white: black ratio is approximately 5:1, while the male: female incidence ratio is 8:1 [72]. The causes of these variations are not well known [73]. Given that the incidence of EAC is rising in tandem with the fast rise in the number of obese people, and that obesity is known to raise the risk of numerous malignancies in Western nations [74], GERD is recognised as a risk factor for EAC. Obesity is also considered to be a risk factor.

Numerous case-control studies provide credence to this theory [77,78]. According to a meta-analysis by Hampel et al., there is a statistically significant increase in the risk for EAC for both being overweight (BMI, 25–30 kg/m2) and obese (BMI > 30 kg/m2) (OR, 1.52; 95% CI, 1.147–2.009 vs. OR, 2.78; 95% CI, 1.850–4.164, respectively).

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The oesophageal squamous epithelium is replaced by a metaplastic columnar cell-lined epithelium in BE, the condition from which most EACs arise. Histologically, the metastasis-dysplasia-carcinoma sequence correlates the progression of BE to adenocarcinoma." 10% of people with GERD go on to develop BE, and GERD is a risk factor for BE. In patients with BE, the annual incidence of adenocarcinoma development is 0.3%–1% [79]. As a result, obesity may be tangentially linked to BE because, as was previously mentioned, it may be a risk factor for GERD. Furthermore, obesity may directly affect the susceptibility for advancement to oesophageal cancer, even if it is uncertain what causes the conversion of a benign oesophageal epithelium to a malignant epithelium.

High BMI may accelerate the development of BE into EAC [80], according to an epidemiological study. While 60% of people with EAC have reportedly experienced GERD symptoms in the past, 40% have never experienced reflux symptoms [81]. Adenocarcinoma after BE can occasionally be found in asymptomatic individuals [82], and some people do not exhibit GERD symptoms [59,60]. Identification of risk factors for BE other than GERD would be very helpful in the identification of asymptomatic BE and EAC. However, these risk variables are not well recognised. There are few studies examining the relationship between obesity and BE risk.

While Chak et al. [83] demonstrated that obesity was linked to the length of obesity rather than the presence of BE, Stein et al.[84] observed that obese patients are more likely to develop BE. According to Smith et al. [85], BE was significantly more likely among individuals with GERD symptoms who were obese, although obesity by itself did not cause this increase. It is still debatable if obesity poses a separate risk for BE. There is evidence that the obesity pattern affects the risk of several diseases. Compared to those with peripheral obesity, those with visceral obesity are more likely to develop insulin resistance syndrome and cardiovascular disease. In their investigation of the relationship between the pattern of obesity and BE development, El-Serag et al. [86-88] found a strong correlation between a higher risk of BE and both BMI and the surface areas of visceral adipose tissue (VAT), as determined by computed tomography scanning. When BMI was taken into account, VAT continued to have an independent relationship with BE, but the substantial correlation between BMI and BE vanished. In contrast to a greater BMI, a higher [89] WHR was significantly associated with increased chances of aneuploidy, loss of heterozygosity at chromosome 17p (17pLOH), and 9pLOH, all of which have been shown or considered to be predictive of further cancer development from BE [90]. Visceral obesity may therefore have a significant role in raising the risk of BE and encouraging BE to develop to EAC. The gender difference in EAC (male predominance) can be partially explained by the higher prevalence of visceral obesity in males.

The primary causes of gastric reflux disease (GERD) are increased transient lower oesophageal sphincter (LES) [91,92] relaxation, hypotensive LES tone, and hiatal hernia. Moreover, disorders in salivary production, aberrant motility [93-95] of the oesophagus and stomach, or compromised mucosal defence [96] mechanisms can alter the extent of acid reflux injury. Obesity is thought to contribute to GERD, BE, and EAC through a number of pathways. Increased intra-abdominal pressure from obesity may result in an increase in intragastric pressure, which in turn may cause an increase in the gastroesophageal pressure gradient that causes LES relaxation [97]. Furthermore, obesity can cause an increase in intra-abdominal pressure, which can lead to the formation of a hiatal hernia and the displacement of the LES [98].

Consequently, the size of the hernia influences LES pressure and is a substantial independent risk factor for hiatal hernia. It also predicts the severity of esophagitis. The gastroesophageal pressure gradient and intragastric pressure [99,100] are related to both BMI and WC, however WC has recently been shown to have a larger correlation than BMI [101].

Thus, it is possible that visceral fat deposition plays a significant role in the development of GERD. Oestrogen may be involved in the relationship between BMI and GERD symptoms since it is higher in premenopausal women than in postmenopausal women [102]. Furthermore, increased serum levels of adipokines, such as interleukin (IL)-6 and tumour necrosis factor (TNF)-α, [103] are strongly linked to adipose tissues, particularly visceral adipose tissues, which are metabolically active and may contribute to GERD or the ensuing carcinogenesis. Adipose tissues release leptin primarily, and blood levels rise in direct proportion to body fat [104] accumulation. It has been demonstrated that leptin promotes cell division and prevents apoptosis in EAC cells generated from Barrett's [105]. As genetic defects accumulate and remain, the traits of reduced apoptosis and enhanced proliferation, which are frequently observed in BE, play a crucial role in the development of cancer.

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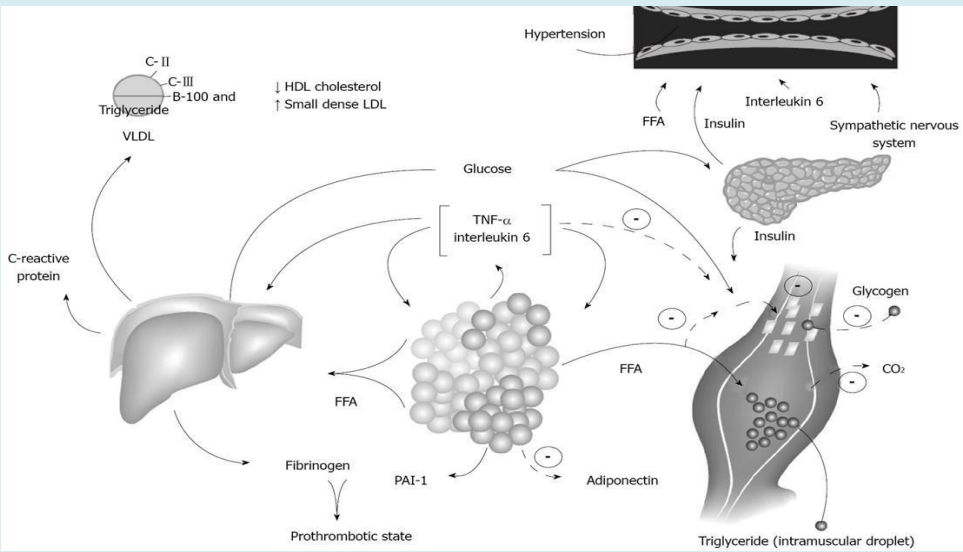

Figure 7: Pathophysiology of the Metabolic Syndrome (Insulin Resistance) Gastric Cardiac Adenocarcinoma and Colorectal Cancer.

There has been a rise in the prevalence of cardiac adenocarcinomas. There have been contradictory findings from a number of researches looking at the relationship between obesity and the risk of cardiac adenocarcinoma [106].

While some discovered either no association or a negative one, others reported an association with an increased risk of cardiac adenocarcinoma [107]. A 2006 meta-analysis revealed that there was heterogeneity in the overall association between high BMI and cardiac adenocarcinoma, and that in certain populations from the United States or Europe, a high BMI was weakly associated with the risk of cardiac adenocarcinoma (OR 0.5; 95%CI, 1.3–1.8); Chinese studies, on the other hand, did not reveal this association [108]. A diverse overall connection was also revealed by a meta-analysis conducted in 2005.

As such, there is ongoing debate over the relationship between obesity and the risk of cardiac adenocarcinoma.

With around 52,000 [109] fatalities each year from cancer, colorectal cancer is the second most common cause of cancer-related mortality in the US. Although a number of dietary and lifestyle factors, as well as a family history, have been associated to an increased risk [110,111] of colorectal cancer, the exact origins of the disease are still unknown. Numerous studies have demonstrated that there is a correlation between a higher BMI and a higher risk of colorectal cancer, particularly in men [111]. Furthermore, Giovannucci et al. [112] showed that elevated WC and WHR values were significant risk factors for colorectal malignancies. The relative risk of colorectal cancer for WHR ≥ 0.99 compared to WHR < 0.90 was 3.41 (95% CI, 1.52–7.66) and for WC ≥ 43 inches (about 109 cm) compared to WC < 35 inches (approximately 89 cm) was 2.56 (95% CI, 1.33–4.96). The relative risk of colorectal cancer for WHR ≥ 0.99 compared to WHR < 0.90 was 3.41 (95% CI, 1.52–7.66) and for WC ≥ 43 inches (about 109 cm) compared to WC < 35 inches (approximately 89 cm) was 2.56 (95% CI, 1.33–4.96). Additionally, Schoen et al. [113] showed a significant correlation between higher WC measures and colorectal cancer. Given the higher prevalence of visceral obesity in males compared to women, it is believed that visceral obesity acts as a mediating factor between BMI and the elevated risk of colorectal cancer. Given that a malignant illness frequently affects a host's body weight, anthropometric measurements in individuals with confirmed colorectal cancer are unlikely to be significant. Due to this, research has been done on the relationship between obesity and colorectal adenomas, which are known to be precancerous lesions of the colon and rectum [114]

According to Giovannucci et al., [115] BMI was not significantly related to an elevated risk of distal colon adenoma, regardless of size, whereas WC and WHR were unrelated to small adenomas with diameter less than 1 cm but major risk factors for large distal colon adenomas with diameter > 1 cm. Distal colon cancer has been observed to have a somewhat greater correlation between WC and an elevated risk of cancer.

When obesity functions as a risk factor for colon cancer, the degree of involvement may vary depending on the colon's specific sections [116].

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A significant contributing factor to the carcinogenesis of colon cancer has also been proposed to be being overweight during adolescence and into adulthood. Because there are so many confounding variables, it is difficult to investigate the relationship between obesity and the risk of colorectal cancer [117,118]. Therefore, additional sub analyses are required.

Research has examined the correlation between several components of the metabolic syndrome and the risk of colorectal cancer. With proximal colon cancer being more likely, type 2 diabetes raises the risk of colon cancer by 1.3 to 1.6 times. It is unknown how insulin plays a part in the correlation between diabetes mellitus and a higher risk of colorectal cancer [119]. The relationship between high serum insulin levels and an increased risk of colorectal cancer is still unclear, despite Yoshida et al. [120] reporting a direct correlation between the presence of adenoma and hyperplastic polyps in the proximal colon and insulin levels [120,121]. Numerous researchers looked into the possible link between elevated HDL cholesterol and triglycerides and the risk of colorectal cancer, but the findings were inconsistent, requiring more investigation [121-123]. Ahmed et al. investigated the possibility of metabolic syndrome as a colorectal cancer risk factor [124]. Age- and sex-adjusted colorectal cancer development was positively correlated with metabolic syndrome that met diagnostic criteria, and there was a dose-response relationship observed between the number of metabolic syndrome components and colorectal cancer development. Metabolic syndrome has been demonstrated to be a risk factor for colon cancer development in males but not in women, according to sex distribution study. In contrast to patients without polyps, Wang et al. [125-127] found that the OR of developing colorectal adenoma increased gradually with the amount of metabolic syndrome components present. For colorectal cancer, obesity is a significant risk factor. Adipose tissue, particularly VAT, is not just a tissue that stores fat; it is also a metabolically active organ that secretes several adipokines, which are proteins that are produced and secreted by adipocytes [128]. Examples of these proteins include TNF-α, IL-6, and adiponectin. Growth factors like insulin-like growth factor-1 (IGF-1), which is made in the liver, are also found in adipose tissue [128,129]. Insulin resistance syndrome has been related to several molecules released by adipose tissue, including TNFα, IL-6, and adiponectin. Consequently, there is a substantial correlation between obesity and insulin resistance [128], a condition characterised by high levels of both insulin and IGF1. In vitro, insulin plays a crucial role in the growth of colonic mucosal cells and colonic carcinoma cells [129].

IGF-1 [130,131] also inhibits apoptosis and accelerates the advancement of the cell cycle, which ultimately results in the development of cancer.

The relationship between hyperinsulinemia and colorectal neoplasm is unknown, however it is known that insulin has anti-inflammatory properties, and anti-inflammatory drugs have been demonstrated to lower the risk of colorectal neoplasm. Furthermore, adipose tissue has been proposed as the mediating factor in the relationship between obesity and tissue inflammation. Since ulcerative colitis patients acquire colorectal cancer due to chronic inflammation, it is hypothesised that this subclinical inflammation plays a role in the development of colorectal cancer [132].

Conclusion

Numerous gastrointestinal disorders seem to be associated with obesity, particularly visceral obesity. Since visceral obesity is the main component of metabolic syndrome, gastrointestinal disorders may be linked to metabolic syndrome. The relationships between specific elements of the metabolic syndrome, other than obesity, and gastrointestinal disorders have not been thoroughly investigated. According to recent research, diseases of the digestive system, such as upper gastrointestinal disorders, are associated with MS and visceral obesity in addition to arteriosclerotic and ischemic heart disease. As a result, it is concerning that there are more people with MS. There are recognised differences in the prevalence of MS and obesity according to gender, ethnicity, and geography. A cluster of metabolic abnormalities that meet the diagnostic criteria of metabolic syndrome may raise the risk of gastrointestinal diseases more than an individual metabolic abnormality because each component of metabolic syndrome may interact to increase the risk of gastrointestinal diseases.

The complex interplay between metabolic syndrome and upper gastrointestinal (GI) diseases underscores the importance of understanding metabolic syndrome as a multifaceted risk factor.

Metabolic syndrome, characterized by a cluster of conditions including insulin resistance, central obesity, dyslipidaemia, and hypertension, has been increasingly associated with various upper GI diseases such as gastroesophageal reflux disease (GERD), Barrett's oesophagus, and oesophageal adenocarcinoma.

Research indicates that the pro-inflammatory state induced by metabolic syndrome exacerbates mucosal damage and impairs the healing process in the upper GI tract. The presence of central obesity and insulin resistance, key components of metabolic syndrome, are particularly implicated in the pathogenesis of GERD due to increased

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intra-abdominal pressure and altered oesophageal motility. Furthermore, the chronic low-grade inflammation characteristic of metabolic syndrome can contribute to the progression from GERD to Barrett's oesophagus and eventually oesophageal adenocarcinoma.

The bidirectional relationship between metabolic syndrome and upper GI diseases suggests that management strategies should address both conditions concurrently. Lifestyle interventions, including dietary modifications, increased physical activity, and weight loss, have shown promise in mitigating the effects of metabolic syndrome and, subsequently, reducing the incidence and severity of upper GI diseases. Pharmacological treatments targeting the individual components of metabolic syndrome, such as antihypertensive and lipid-lowering agents, may also play a role in reducing upper GI disease risk.

In conclusion, the influence of metabolic syndrome on upper gastrointestinal diseases is profound and multifactorial. Effective management of metabolic syndrome can potentially alleviate the burden of upper GI diseases, highlighting the need for an integrated approach in both prevention and treatment. Future research should continue to explore the underlying mechanisms linking these conditions and develop targeted interventions to improve patient outcomes.

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