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CLINICAL REVIEW

Influence of metabolic syndrome on upper gastrointestinal disease

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Abstract A recent increase in the rate of obesity as a result of insufficient physical exercise and excess food consumption has been seen in both developed and developing countries throughout the world. Additionally, the recent increased number of obese individuals with lifestyle-related diseases associated with abnormalities in glucose metabolism, dyslipidemia, and hypertension, defined as metabolic syndrome (MS), has been problematic. Although MS has been highlighted as a risk factor for ischemic heart disease and arteriosclerotic diseases, it was also recently shown to be associated with digestive system disorders, including upper gastrointestinal diseases. Unlike high body weight and high body mass index, abdominal obesity with visceral fat accumulation is implicated in the onset of various digestive system diseases because excessive visceral fat accumulation may cause an increase in intra-abdominal pressure, inducing the release of various bioactive substances, known as adipocytokines, including tumor necrosis factor-α, interleukin-6, resistin, leptin, and adiponectin. This review article focuses on upper gastrointestinal disorders and their association with MS, including obesity, visceral fat accumulation, and the major upper gastrointestinal diseases.

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Introduction

Metabolic syndrome (MS) is defined as the accumulation of visceral fat with lifestyle-related diseases associated with abnormalities in glucose metabolism, dyslipidemia, and hypertension. The diagnostic criteria for MS adopted by the Adult Treatment Panel (ATP) III [1] and the International Diabetes Federation (IDF) [2] (Fig. 1) have been used worldwide, while the MS criteria proposed by a joint committee of eight Japanese medical societies in 2005 [3] (Fig. 2) are often used in Japan. Component factors of each MS criteria are waist circumference (WC) beyond the standard value of each diagnostic criteria for MS, and the presence of two or more of the following: (1) dyslipidemia, i.e., low high-density lipoprotein (HDL) cholesterol and/or elevated triglycerides (TG), or medication for dyslipidemia; (2) impaired glucose tolerance, i.e., elevated fasting plasma glucose (FPG), or medication for diabetes; and (3) hypertension, i.e., elevated blood pressure, or medication for hypertension. The recent increase in the number of individuals with MS due to lifestyle changes such as increased fat intake and lack of exercise has been problematic in countries with both advanced and emerging economies. The altered secretion of adipocytokines from visceral fat in persons with MS is related to various pathophysiological conditions, including insulin resistance (Fig. 3). Because it leads to various diseases, such as ischemic heart disease and digestive system disorders, including upper gastrointestinal diseases (Fig. 3), MS has a large impact on public health and medical costs. Here, we review the influence of MS, including obesity and visceral

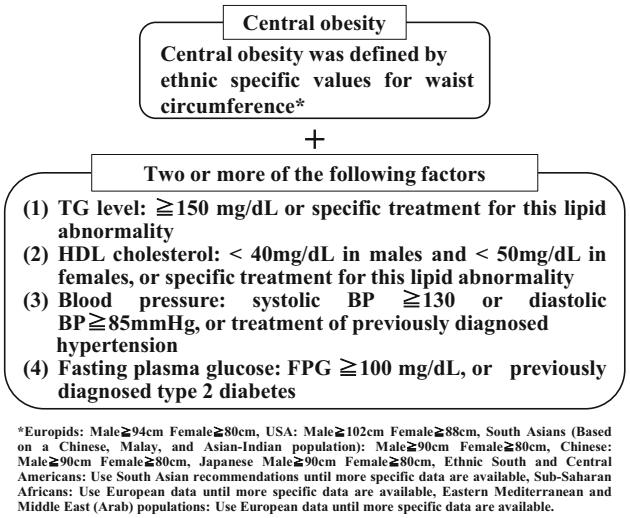

Fig. 1 The criteria for metabolic syndrome proposed by the International Diabetes Federation. *TG* triglycerides, *HDL* high-density lipoprotein, *BP* blood pressure, *FPG* fasting plasma glucose

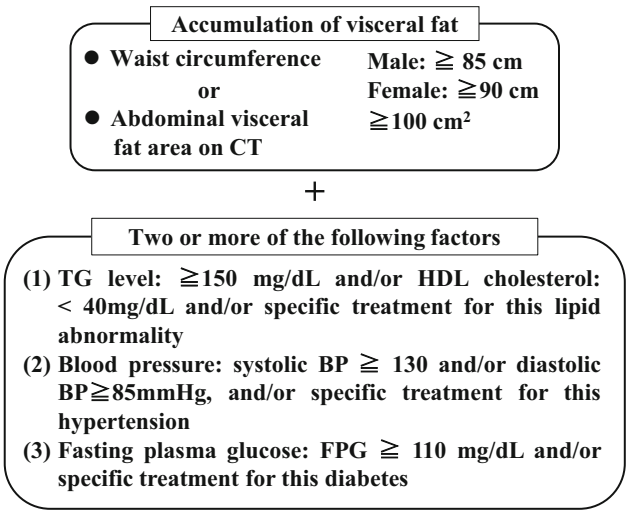

Fig. 2 The MS criteria proposed by a joint committee of eight Japanese medical societies in 2005. *CT* computed tomography, *TG* triglycerides, *HDL* high-density lipoprotein, *BP* blood pressure, *FPG* fasting plasma glucose

fat, on the major upper gastrointestinal diseases, based on studies to date.

Hiatal hernia

Hiatal hernia (HH) is a condition in which elements of the abdominal cavity, most commonly the stomach, herniate through the esophageal hiatus into the mediastinum [4]. The disorder is largely grouped into two categories: the sliding hernia type, which involves a widening of the muscular hiatal tunnel and circumferential laxity of the phrenoesophageal membrane, allowing a portion of the gastric cardia to herniate upward; and the paraesophageal hernia type, which involves either the inversion of the stomach as it herniates or involvement of other organs [5, 6]. HH is generally diagnosed using the barium swallow examination, which demonstrates the amount and position of the stomach within the thorax. In addition, endoscopy is often used for the diagnosis of sliding hiatus hernia, which is diagnosed when the apparent separation between the squamocolumnar junction and the diaphragmatic impression is greater than 2 cm, as measured using the hash marks on the endoscope relative to the incisors.

The prevalence of HH in the general population has been reported in a range of approximately 10 to 50 % [5, 7]. In patients among eastern and western populations undergoing endoscopy, HH was reported at rates of 2.2–17 % [8, 9] and 6.6–22 % [10, 11], respectively. The difference between eastern and western populations may be attributable to lifestyle, genetics, habitus variations, and rates of obesity. In addition, the sliding hernia type accounts for more than 85 % of HH [12], whereas the paraesophageal type has been reported in 3.5–5 % of all HH-related surgery [13].

Obesity is an independent risk factor for the development of both HH and gastroesophageal reflux disease (GERD) [14]. The prevalence of HH in obese individuals has been reported at approximately 5–50 % [15, 16]. In a recent study of 181 morbidly obese patients, Che et al. [17] found that HH was present in 37 %, based on preoperative upper gastrointestinal contrast examination. In the same study, the rates of small and moderate or large HH were 32.6 and 4.4 %, respectively. While the mechanisms controlling the development of HH are currently unclear, several factors have been speculated to contribute. Varela et al. found that intra-abdominal pressure in morbidly obese patients was 2–3 times as high as that in non-obese individuals [18]. In a study using upper gastrointestinal endoscopy, Wilson et al. reported that the prevalence of HH in obese individuals was four times that in normal-weight individuals [19]. In addition, in a recent study including 62 women who underwent either laparoscopic gastric bypass surgery or adjustable gastric banding, Frezza et al. found that body mass index (BMI) correlated with opening abdominal pressure in a linear regression accounting for age and race [20], with an average 0.07-mmHg increase in opening pressure for every 1 kg/m^2 increase in BMI. These findings suggest that the presence of increased intra-abdominal pressure in obese individuals may increase their risk of developing HH. In addition, anatomically, the amount of elastic tissue in the phrenoesophageal membrane progressively declines and laxity increases with age, possibly contributing to the development of HH [4, 21, 22]. Other factors, including esophageal

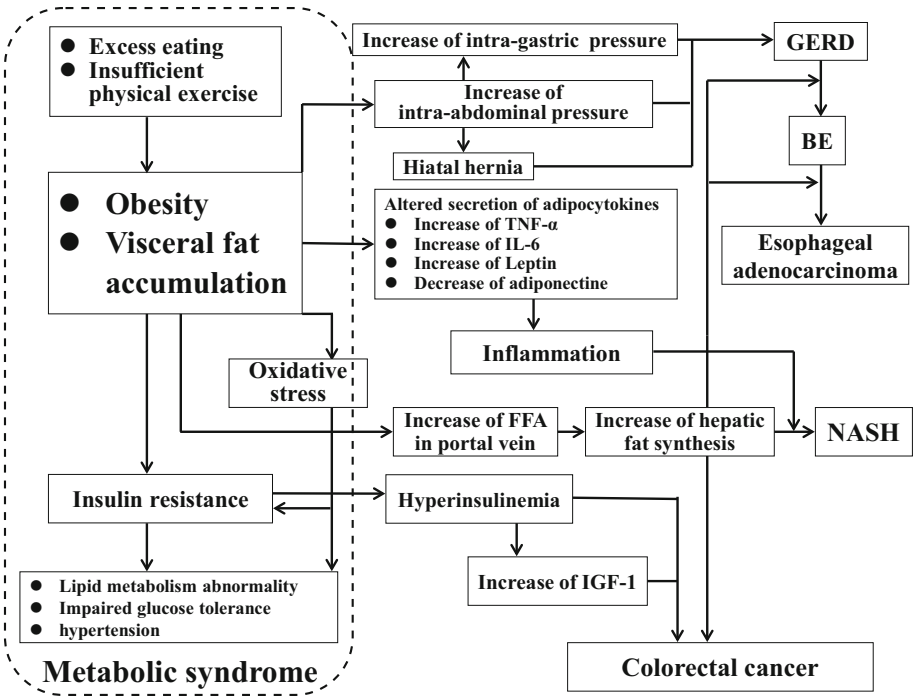

Fig. 3 Hypothesis of mechanisms by which metabolic syndrome, including obesity and visceral fat accumulation, may influence digestive organ diseases. *GERD* gastroesophageal reflux disease, *BE* Barrett's esophagus, *NASH* nonalcoholic steatohepatitis, *TNF-α* tumor necrosis factor-α, *IL-6* interleukin-6, *FFA* free fatty acid, *IGF-1* insulin-like growth factor-1

shortening secondary to chronic GERD and congenital abnormalities, may also play a role in the development of HH by altering the function of the lower esophageal sphincter (LES) [17, 23].

Gastroesophageal reflux disease

GERD is caused by the abnormal reflux of gastric contents into the esophagus, and can be divided into erosive and non-erosive types. Erosive GERD is defined by the presence of esophageal mucosal injury, whereas non-erosive GERD is characterized by the absence of esophageal mucosal injury and the presence of reflux symptoms. GERD is the most common upper gastrointestinal disease in western countries, including the USA, with a reported prevalence of 10 to 30 % [24, 25]. The rates of GERD are lower in Asia, including Japan, reported at between 5 and 10 % [24, 26].

Several studies have shown GERD to be closely associated with obesity. The prevalence of obesity and GERD in the USA has increased to approximate 30 and 20 %, respectively [25, 27, 28]. In developed countries including Japan, many studies have reported that obesity and BMI are strongly related to GERD symptoms [29, 30], although findings in other studies have differed [31, 32]. Thus the association between obesity, including higher BMI, and GERD symptoms is controversial. While some studies have reported that obesity is associated with an increased risk of GERD, the association between MS, including MS components, and GERD is unclear. Several recent studies have focused on the relationship between MS and GERD. Waist circumference, which is used for the assessment of central obesity, has been reported to be associated with esophageal acid exposure to the same extent as BMI. In a cross-sectional study including 100 consecutive patients who underwent 24-h pH monitoring, Kallel et al. reported that, among the five components of MS, abnormal WC and elevation of fasting glucose levels were significant independent factors associated with GERD [33]. In addition, MS, but not BMI, was associated with GERD, confirming the hypothesis that central obesity is associated with GERD. In a case–control study including 1679 cases of erosive esophagitis, multiple regression analysis of various factors showed that MS was a significant independent risk factor [odds ratio (OR) 1.25, 95 % confidence interval (CI) 1.04–1.49] [34]. The study also showed that increased WC was a risk factor for erosive esophagitis, among a number of other components associated with MS, including hypertension, diabetes mellitus (DM), elevated FPG, increased TG, and low HDL cholesterol (OR 1.33, 95 % CI 1.15–1.54). In a study of the influence of metabolic risk factors on the natural course of GERD, Lee et al. suggested that intraesophageal damage may be a dynamic and migratory process in which MS is associated with accelerated progression to or attenuated regression from erosive states [35]. Additionally, MS independently increased the likelihood of progression from a non-erosive to an erosive stage of GERD and/or lowered the likelihood of disease regression in a study of 3669 subjects undergoing repeated

upper endoscopy [relative risk (RR) 1.75, 95 % CI 1.29–2.38]. These reports suggest that MS, abdominal obesity, and WC influence GERD to a greater degree than simple obesity revealed through elevated BMI.

The increase in the prevalence of GERD and obesity in western countries suggests a pathogenetic link and common mechanisms between these two diseases [36]. Although various pathogenetic mechanisms of GERD, including disturbance of the LES, increased gastric acid production, increased intragastric pressure, and esophageal acid exposure, have been speculated to be associated with obesity and to play an important role in the development of GERD [30, 37–40], the exact pathophysiological mechanisms underlying the association between GERD and obesity have not been fully identified. Obesity and visceral fat, evidenced by increased WC, may increase intra-abdominal pressure. Studies have found that increased intra-abdominal pressure was directly responsible for increased extrinsic gastric compression and heightened gastroesophageal pressure gradient [40] by increasing intragastric pressure [41, 42]. In addition, GERD may be advanced by the development of HH [43, 44]. However, the assessment of the abdominal cavity is difficult due to the influence of various organs and the change in intestinal pressure. Therefore, the abdominal cavity may not be considered a limited space, and novel methods for accurately evaluating the abdominal cavity are needed. Also, the association between erosive esophagitis and the amount of visceral adipose tissue may be influenced not only by simple mechanical aspects, such as increased abdominal pressure and gastric hypersecretion, but also by metabolic and inflammatory pathways. Individuals with MS or visceral fat-dominant obesity are likely to exhibit GERD or erosive esophagitis [34–37, 45]. Visceral adipose tissue is a source of inflammatory cytokines and is associated with systemic inflammation in obese individuals [46, 47]. Systemic low-grade inflammation, as observed in obesity with visceral adipose tissue, may interact with or even enhance other inflammatory conditions such as esophagitis [48, 49]. Various products of the adipose tissue, known as adipocytokines, have been characterized [50]. Tilg et al. proposed that adipocytes and infiltrating macrophages in visceral adipose tissue produced a large amount of systemically active mediators, including adipocytokines, thought to contribute to low-grade inflammation observed in severe obesity, MS, and other associated disorders [48]. Various mediators released by visceral adipose tissue, including adiponectin, leptin, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), may exert distal effects in the stomach and/or esophagogastric junction. The proinflammatory cytokines IL-1 and TNF-α have both been reported to stimulate gastrin release in human gastric antral fragments [51, 52]. Thus, proinflammatory mediators such as adipocytokines may exacerbate and perpetuate local inflammation at the esophagogastric junction after local injury resulting from pathologic levels of esophageal acid exposure.

Previous reports have shown that visceral adipose tissue, rather than BMI and WC, play a key role in the association between MS and GERD [53, 54]. Nam et al. analyzed the association between obesity, including abdominal visceral adipose tissue volume, and erosive esophagitis in a prospective health screening cohort study of 4274 patients who underwent esophagogastroduodenoscopy and computed tomography [54]. The authors found that the multivariate OR for erosive esophagitis was 1.97 (95 % CI 1.34–2.90, P <0.001) for visceral adipose tissue volume of 500–999 cm^3, 2.27 (95 % CI 1.51–3.39, P <0.001) for 1000–1499 cm^3, and 2.94 (95 % CI 1.87–4.62, P <0.001) for more than 1500 cm^3, compared with participants who had visceral adipose tissue volumes of less than 500 cm^3. In addition, BMI, WC, and visceral and subcutaneous adipose tissue volume were significantly associated with erosive esophagitis in men; however, only visceral adipose tissue volume was associated with erosive esophagitis in women. Sogabe et al. reported a significantly higher prevalence of erosive esophagitis in visceral fat-type than in subcutaneous fat-type, and visceral fat-type was a significant predictor of an increased prevalence of erosive esophagitis in men with MS; however, there was no significant difference in the prevalence of erosive esophagitis between visceral fat-type and subcutaneous fat-type in women with MS [53, 55]. This discrepancy between men and women may reflect the difference in adipose tissue distribution [56], estrogen-related sex hormones, treatment for lifestyle-related disease, and other social lifestyle factors.

Barrett's esophagus

Barrett's esophagus (BE) is a condition wherein the normal distal esophageal squamous epithelium is replaced by columnar-type mucosa, including columnar metaplastic epithelium characterized by the presence of mucus-secreting goblet cells. The relative risk of adenocarcinoma among patients with BE has been reported at 11.3 (95 % CI 8.8–14.4) compared with the general population [57], and the annual incidence of adenocarcinoma developing in patients with BE is 0.3–1 % [58–60]. Thus, BE may be recognized as a precancerous lesion for esophageal adenocarcinoma [61]. Aging, male sex, white race, the duration and severity of GERD, and obesity have also been speculated to be risk factors for the development of BE [62, 63].

Several epidemiologic studies have shown that BE is strongly associated with obesity, and abdominal obesity in particular [64, 65]. In a meta-analysis of 15 independent

studies, Singh et al. reported that patients with central adiposity had a higher risk of BE (adjusted OR 1.98, 95 % CI 1.52–2.57) than patients with normal body habitus [65]. Furthermore, in a retrospective cross-sectional study of male patients who underwent upper endoscopy, Stein et al. reported that mean BMI was significantly higher in patients with BE than in those without BE, and OR for the presence of BE was 2.43 (95 % CI 1.12–5.31) for subjects with a BMI of 25–30 kg/m^2, versus 2.46 (95 % CI 1.11–5.44) for subjects with a BMI of more than 30 kg/m^2 [66]. Chak et al., however, reported no significant difference in the proportion of obese patients with symptomatic gastroesophageal reflux disease with and without BE at the time of study enrollment and at 1 and 5 years later [67]. Although a greater number of studies have reported an association between BE and obesity than have reported no association, it remains controversial whether obesity is an independent risk factor for BE. Based upon the findings of upper endoscopy, BE was recently classified into short-segment BE (SSBE), which is less than 3 cm, and long-segment BE (LSBE), which is 3 cm or greater. The prevalence of LSBE is known to be lower in Asian countries, including Japan, than in western countries, although SSBE is more common in two areas [68]. LSBE reportedly carries a greater risk of progression to dysplasia and esophageal adenocarcinoma than SSBE in patients with BE without dysplasia [63, 69]. In a population-based study that included 381 patients diagnosed with BE, Abdallah et al. found that mean BMI was significantly higher in patients with LSBE than in those with SSBE, and the authors reported a significant correlation between BMI and the length of BE [63]. However, other studies have shown no significant correlation between BMI and the length of BE [66, 70], and many such studies have included a small number of patients. At present, the mechanisms controlling BE length and the relationship between BE length and BMI are unclear.

Several groups have reported a positive correlation between obesity with GERD symptoms and the risk of developing BE. In an Australian case–control study population, Smith et al. reported that obese subjects with GERD symptoms had a markedly higher risk of developing BE (OR 34.4, 95 % CI 6.3–188) than those with reflux alone (OR 9.3, 95 % CI 1.4–62.2) or obesity alone (OR 0.7, 95 % CI 0.2–2.4) [71]. The effect of central adiposity on the risk of developing BE was reported in several studies of patients with GERD [45, 72–74]. These studies suggest that central adiposity rather than overall obesity may have a GERD symptom-independent effect on the development of esophageal metaplasia. On the other hand, in a prospective cohort study examining the potential difference in BMI between patients with GERD and patients with BE, obesity was a risk factor for both GERD and BE, although patients with BE did not show increased BMI compared with patients with chronic GERD [75]. While BE is thought to be associated with obesity, especially abdominal obesity [72, 76], the mechanisms underlying this association are unknown. It is possible that abdominal obesity may cause direct mechanical pressure on the stomach, increasing intragastric pressure and leading to more frequent relaxation of the LES and subsequent reflux and esophageal acid exposure [66, 77]. Also, HH may partially explain the association between abdominal obesity and increased risk of BE, as a previous study showed that a strong association between WC and increased separation of the gastroesophageal pressure components indicated enlargement of the HH [78]. In addition, it has been reported that the prevalence of HH, including large HH, was significantly higher in patients with erosive esophagitis and BE than in GERD patients without BE [19, 79]. The volume of abdominal fat, which includes the subcutaneous and visceral fat, may increase the risk of developing BE. In particular, visceral abdominal fat has been shown to release several proinflammatory cytokines, including IL-6 and TNF-α [66, 80]. These cytokines can reduce serum adiponectin, producing an anti-apoptotic and antiproliferative effect. As a result, visceral abdominal fat may aggregate, increasing inflammation and thus the development of BE.

Esophageal adenocarcinoma

Although the incidence of several cancers has decreased over the past few decades, the rate of esophageal adenocarcinoma (EAC) has increased dramatically in developed countries [81, 82]. The prevalence of obesity in developed countries has similarly increased within this time period. The higher rates of obesity may be linked to an increased risk of several cancers, including EAC [83, 84]. A BMI greater than 25 kg/m^2 was reportedly associated with an increased risk of EAC in both men (OR 2.2, 95 % CI 1.7–2.7) and women (OR 2.0, 95 % CI 1.4–2.9) in a systematic review and meta-analyses including 14 studies and 2488 patients with EAC [64]. Obesity has been recognized as a risk factor for EAC based on the findings of several studies showing an association between obesity and EAC. Visceral obesity in particular is thought to be influential in the development of GERD, BE, and EAC. In a case–control study within 206,974 cohort members, including 101 incidents of EAC, Douglas et al. reported that the risk of EAC was higher in individuals with an abdominal diameter of more than 25 cm versus a diameter of less than 20 cm (OR 3.47, 95 % CI 1.29–9.33) [85]. The authors also concluded that increasing abdominal diameter was associated with an increased risk of EAC, independent of BMI. Abdominal obesity, rather than simple obesity or total

obesity, may affect the risk of EAC, as abdominal obesity is also reportedly an independent risk factor for progression from BE to EAC [86].

The diagnostic criteria for MS requires a greater standard value than for WC, with two or more of the following components: dyslipidemia, impaired glucose tolerance, and hypertension. Although obesity is known to be associated with an increased risk of EAC, the role of MS and metabolic factors in the etiology of EAC is unclear. BMI was associated with an increased risk of EAC (RR 7.34, 95 % CI 2.88–18.7) top versus bottom quintile in a prospective cohort study of MS and cancer among 578,700 individuals in Austria, Norway, and Sweden, including 114 EAC patients [87]. In the same study, composite MS score was associated with a risk of developing EAC (RR 1.56, 95 % CI 1.19–2.05) per one unit increase in *z*-score. Another large nationwide cohort study based on the data from 11 prospective population-based cohorts in 192,903 participants, including 62 who developed EAC, showed that increased WC was associated with EAC (HR 2.48, 95 % CI 1.27–4.85) [88]. However, MS, consisting of four components—hypertension, lower-HDL cholesterol, hyper-TG, and hyper-fasting plasma glucose—was not significantly associated with an increased risk of EAC (HR 1.32, 95 % CI 0.77–2.26), and none of the four MS components was significantly associated with a higher risk of EAC. There are several potential mechanisms underlying the positive association between WC, which is a major component of MS, and risk of EAC. Increased intra-abdominal pressure caused by abdominal obesity, as evidenced by a high WC, may increase the risk of gastroesophageal reflux, a strong risk factor for EAC [89–91]. In addition, abdominal obesity evidenced by a high WC may be associated with increased hormone levels such as insulin-like growth factor (IGF) and adiponectin, which are known to influence cell division, cell death, and healing [92, 93]; as a result, WC may be associated with the risk of developing EAC. Components of MS other than WC thus may not influence the incidence of EAC, unlike abdominal obesity with a high WC.

Gastritis

Previous studies have shown an inverse association between low pepsinogen (PG) I/II and increased BMI [94, 95]. In contrast, BMI was positively associated with the occurrence of atrophic gastritis among a group of 35–44-year-old patients in a study in northern Sweden [96]. A Japanese study also showed that low PGI–PGI/PGII, which is thought to be a marker for chronic atrophic gastritis, may be independently associated with both low body weight and obesity in Japanese men [97]. At this time, the association between BMI and atrophic gastritis remains unclear.

Several studies have investigated the relationship between obesity and erosive gastritis. An upper endoscopy study of a general Korean population reported that overweight, defined as BMI of more than 25 but less than 30 kg/m^2, and obesity, defined as BMI of more than 30 kg/m^2, were significant contributors to the development of erosive gastritis [98]. A logistic regression analysis in 2400 Japanese patients undergoing a health check-up showed that BMI was significantly higher in patients with erosive gastritis than in those without, and that BMI was a significant factor in the development of erosive gastritis [99]. The authors speculated that the erosive gastritis may be related to excess gastric acid due to the location of endoscopic erosive gastritis. In the same study, the rate of endoscopic erosive gastritis gradually increased as the adiponectin level decreased, suggesting that adiponectin may protect the stomach from excessive gastric acid through its anti-inflammatory effects.

Several studies have reported a relationship between obesity and histologic gastritis, defined as the presence of inflammation of the gastric mucosa [100]. In a study of the endoscopic and histologic findings of the foregut in morbidly obese patients, Csendes et al. showed a high degree of abnormal pathology in the antral mucosa [101], with antral mucosa in chronic active superficial gastritis, chronic inactive superficial gastritis, and atrophic gastritis with intestinal metaplasia found in 53.0, 8.6, and 6.5 % of morbidly obese patients, respectively. Additionally, endoscopic biopsy revealed that 27.5 % of consecutive morbidly obese patients whose BMI was more than 40 kg/m^2 showed erosions in the stomach, and 62 % of morbidly obese patients who had undergone antral biopsies had histologic chronic superficial gastritis in the gastric antrum. Another study reported that the prevalence of histologically identified gastritis preoperatively in morbidly obese patients was significantly higher than in age- and sex-matched control subjects with a normal BMI [23]. In addition, the prevalence of *Helicobacter pylori* (*H. pylori*) infection in morbidly obese patients did not differ from that in non-obese control patients. Thus, obesity rather than *H. pylori* infection may induce histologic gastritis in morbidly obesity patients.

Peptic ulcer

Although *H. pylori* infection and non-steroid anti-inflammatory drugs are related to peptic ulcer disease, the relationship between obesity and peptic ulcers remains controversial. Several recent studies have linked obesity with susceptibility to mucosal injury, including peptic

ulcers. Assef et al. found upper gastrointestinal endoscopy-diagnosed peptic ulcers in 57.1 % of 30 severely obese patients who underwent upper endoscopy before bariatric surgery, although the frequency of peptic ulcers was no higher in obese patients (mean BMI of 47.26 kg/m^2) than non-obese individuals (BMI of 24.21 kg/m^2) [102]. Dietz et al., on the other hand, reported that among 126 obese patients who had undergone upper gastrointestinal endoscopy for the preoperative evaluation of bariatric surgery, gastric and duodenal ulcers were found in 2.4 and 0.8 %, respectively [103].

There are also several reports of peptic ulcers in asymptomatic patients or the general population. In 572 asymptomatic patients undergoing a routine health check-up in Taiwan, Wang et al. reported that the prevalence of gastric ulcers, duodenal ulcers, and both gastric and duodenal ulcers found using endoscopy was 4.7, 3.9, and 0.9 %, respectively, and the OR for the presence of peptic ulcer disease in subjects with a BMI of 25–30 kg/m^2 versus more than 30 kg/m^2 was 1.5 (95 % CI 1.0–2.2) and 3.6 (95 % CI 1.5–8.7), respectively, using multivariate analysis [104]. Another study reported a prevalence of peptic ulcers of 4.1 % (gastric ulcers 2.0 %, duodenal ulcers 2.1 %) in a population of adult patients in northern Sweden who underwent esophagogastroduodenoscopy [105]. In addition, obesity was an independent risk factors for gastric ulcers (OR 4.15, 95 % CI 1.31–13.13), but not duodenal ulcers. Shimamoto et al. investigated 43 individuals with gastric ulcers and 32 with duodenal ulcers in a cross-sectional study of 8013 healthy subjects in Japan who underwent upper gastrointestinal endoscopy [106]. A BMI of more than 25 kg/m^2 was significantly associated with gastric ulcers (OR 1.15, 95 % CI 1.06–1.24), but not duodenal ulcers, using multiple logistic regression analysis. Boylan et al. showed that central and total obesity was associated with increased risk of peptic ulcers in a large prospective cohort of 47,120 male health professionals in the USA [107]. The HR for gastric ulcers was 1.19 (95 % CI 0.83–1.72), 1.52 (95 % CI 1.05–2.19), and 1.83 (95 % CI 1.20–2.78) for obese men with a BMI of 25.0–26.9 kg/m^2, 27.0–29.9 kg/m^2, and more than 30.0 kg/m^2, respectively, compared to men with a BMI of 23.0–24.9 kg/m^2. The HR for gastric ulcers was 1.62 (95 % CI 0.98–2.70), 1.78 (95 % CI 1.06–3.00), and 1.88 (95 % CI 1.06–3.33) for men with waist-to-hip ratios (WHR) of 0.90–0.94, 0.95–0.99, and more than 1.00, respectively, compared to men with a WHR of 0.85–0.89, after multivariate adjustment. In secondary analyses, increased BMI and WHR were both associated with an increased risk of *H. pylori*-negative ulcers; however, the risk of duodenal ulcers was not associated with BMI or WHR. The authors concluded that central and total obesity were associated with an increased risk of peptic ulcers, especially gastric and *H. pylori*-negative ulcers. The association between obesity and peptic ulcers has been widely investigated, and many studies have shown a link between increased BMI or WC and gastric ulcers, but not duodenal ulcers. The mechanisms underlying the link between obesity and peptic ulcers are still unclear, but peptic ulcers may be influenced by low-grade chronic inflammation, known to be associated with obesity [108–111].

Gastric adenocarcinoma

Although the incidence of gastric adenocarcinoma (GAC) has decreased worldwide in recent decades, it remains a major cause of cancer-related mortality [112, 113]. GAC is divided into two types, cardia adenocarcinoma (CAC) and noncardia adenocarcinoma (NCAC), based on the anatomical location of the lesion. Some differences in the epidemiologic and clinical characteristics of CAC and NCAC have been reported. Although the incidence of NCAC has gradually declined as a result of improved public environments, changing lifestyles, and reduced prevalence of *H. pylori*, a concomitant rise in the incidence of CAC has been reported in western countries [114–116]. The cause of this increased risk of NCAC has been reported to be regular tobacco smoking, alcohol consumption, excess salt consumption, and low consumption of fresh fruits and vegetables [117, 118]. A recent study reported that *H. pylori* infection was among the most important factors for increased risk of NCAC [119], whereas the role of *H. pylori* infection in CAC remains unclear [120]. Seropositivity for *H. pylori* was reported to be positively associated with NCAC but inversely associated with CAC [121].

The association between stomach cancer (adenocarcinoma) and obesity varies with types (i.e., anatomical locations) of stomach cancer, such as CAC (cardia adenocarcinoma) and NCAC (noncardia adenocarcinoma). Although several studies have shown an association between obesity and risk of CAC, these findings are controversial [122, 123]. In a meta-analysis, Kubo et al. reported that high BMI was weakly associated with the risk of CAC in limited US and European populations (OR 0.5, 95 % CI 1.3–1.8) [64]. On the other hand, a significant positive association between BMI and CAC was reported in four of six studies reviewed [124]. An association between obesity and stomach cancer, including CAC and NCAC, has been recently reported. Yang et al. reported that excess body weight was associated with an increased overall risk of GAC (OR 1.22, 95 % CI 1.06–1.41) in a systematic review and meta-analysis of published cohort studies, including 9492 GAC cases [125]. Excess body weight in particular was associated with increased risk of CAC (overweight and obese defined as a BMI of more than

25, OR 1.55, 95 % CI 1.31–1.84), but no significant link was found between excess body weight and NCAC (overweight and obese, OR 1.18, 95 % CI 0.96–1.45). In a cohort study among 483,700 participants (290,291 men and 193,409 women), Camargo et al. found that excess body weight was associated with increased GAC risk when all GAC sub-sites were combined (p trend = 0.028) [126]. The risk of CAC in particular was increased with excess body weight, although no consistent association was shown between NCAC and excess body weight. Several recent studies have similarly shown an association between obesity and CAC, but not NCAC.

Several studies have recently investigated the association between GAC and MS. Lin et al. reported that MS was significantly associated with an increased risk of GAC (HR 1.44, 95 % CI 1.14–1.82) in a Norwegian cohort study with 192,903 participants, including 373 with GAC [88]. In this study, the presence of MS was associated with a 64 % increased risk of GAC (HR 1.64, 95 % CI 1.07–2.49) in women, and a 36 % increased risk (HR 1.36, 95 % CI 1.01–1.84) in men. These findings suggest that MS is significantly associated with an increased risk of GAC in both sexes, but that the risk is higher in women than in men. An association was also found between each component of MS and GAC: higher WC (HR 1.71, 95 % CI 1.05–2.80), hypertension (HR 2.41 95 % CI 1.44–4.03), and higher glucose levels (HR 1.74, 95 % CI 1.18–2.56) were significantly associated with a risk of GAC in women. Conversely, no components of MS were associated with risk of GAC in men. These differences between genders may be the result of differences in adipose tissue distribution [56], estrogen-related sex hormones, and social lifestyle factors such as physical activity, exercise, and diet. Chronic inflammation induced by MS and its mediators may be involved in tumor development [127], and may be different between men and women with MS. This study may suffer from selection bias, however, because GAC was not divided into CAC and NCAC. CAC and NCAC are known to differ in clinical and pathological features as well as in prognosis. Although many reports have showed a significant positive correlation between obesity and CAC, it remains unclear whether there is a significant association between MS and CAC or NCAC. O'Doherty et al. showed a positive association between CAC and body weight (HR 2.52, 95 % CI 1.6–4.1), BMI (HR 3.67, 95 % CI 2.0–6.7), and WC (HR 2.22, 95 % CI 1.4–3.5) in a recent large prospective US study with 218,854 participants, including 316 GAC patients [128]. However, there was a consistent association between NCAC and the majority of the anthropometric variables.

Although the mechanisms linking GAC with hypertension are currently unclear, hypertension and malignancy may share similar biochemical pathways. An increase in inositol triphosphate and cytosolic calcium may be involved in the pathogenesis of hypertension and in the early events of cell proliferation [129]. The association between high glucose levels, a component of MS, and GAC has been shown in previous studies [130, 131]. Although the majority of previous studies from Asian countries showed a positive association between high glucose levels or diabetes and GAC [132, 133], other studies from Europe and the USA have failed to find an association [134, 135]. The risk of GAC may also differ between women and men. It was reported that glucose was significantly associated with the risk of GAC in women only [130]. Calculation of standardized mortality rates in a UK cohort study of 28,900 patients with insulin-treated diabetes showed that the risk of GAC mortality and GAC incidence in patients with insulin-treated diabetes was not significantly higher than that in the general population [134]. Similarly, in a cohort study in Scotland including 9577 patients newly diagnosed with type 2 diabetes, the unadjusted and adjusted risk of GAC was not significantly higher in patients with diabetes than in matched non-diabetic controls [135]. Two Japanese studies using the same prospective cohort, however, showed that moderately increased fasting blood glucose [136] and hemoglobin A1c [137] were associated with an increased risk of GAC. A meta-analysis including a total of 7 case–control and 18 cohort studies reported that glucose was shown to be an independent risk factor for GAC and that individuals with diabetes were at increased risk of developing GAC [131]. Although the mechanisms underlying the association between hyperglycemia and GAC are still unclear, several possible pathophysiological mechanisms have been proposed [130]. It was demonstrated that IGF-1, which is generally known to increase cancer risk [138, 139], had a direct mitotic effect in human gastric cancer cell lines [140]. In addition, high serum glucose levels may induce DNA damage and promote cancer development due to the formation of reactive oxygen species [141]. Inconsistent findings among studies investigating the association between glucose levels and GAC may be due to lifestyle differences and differences in insulin sensitivity based on the genetic background of different ethnicities. Gender may also play a role through sex hormones and lifestyle factors such as alcohol consumption and food preference. The mechanisms underlying the role of hyperglycemia in the development of GAC in MS must be further assessed in larger epidemiological and experimental studies.

Conclusion

In this review, we have described the association between upper gastrointestinal diseases and MS, including obesity and visceral fat accumulation. Recent studies have reported

that MS and visceral obesity are associated not only with ischemic heart disease and arteriosclerotic diseases, but also with digestive system organ diseases, including upper gastrointestinal disorders. Accordingly, the increased number of individuals with MS is problematic. The prevalence of MS and obesity is also known to differ by region, ethnicity, and gender [142]. For example, rates of MS in a general Japanese population were reported to be approximately 12.1–18.4 % in men and 1.7–5.8 % in women [143, 144]. In a civilian non-institutionalized US population, on the other hand, rates of MS reported for men and women were 21.8 and 23.7 %, respectively [145]. Visceral fat accumulation has been associated more strongly than obesity with the development of digestive diseases such as NAFLD and erosive esophagitis. MS components may interact to increase the risk of upper gastrointestinal diseases. Although researchers have speculated that the risk of gastrointestinal diseases is increased by exposure to various bioactive substances, known as adipocytokines, which are induced by excessive visceral fat accumulation, there have not yet been sufficient studies to confirm this hypothesis or the mechanism of discrepancy among region, ethnicity, and gender, and further studies are needed to clarify these associations.

Compliance with ethical standards

Conflict of Interest: Masahiro Sogabe, Toshiya Okahisa, Tetsuo Kimura, Koichi Okamoto, Hiroshi Miyamoto, Naoki Muguruma, and Tetsuji Takayama declare that they have no conflict of interest in this manuscript.

Human/Animal Rights: All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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