Review

Metabolic syndrome and gastrointestinal diseases

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Metabolic syndrome is a cluster of metabolic abnormalities consisting essentially of obesity, especially abdominal obesity. Metabolic syndrome has been highlighted as a risk factor for cardiovascular and other chronic diseases. Obesity has been implicated in various gastrointestinal diseases such as gastroesophageal reflux diseases and colorectal cancer. Recently, abdominal obesity has been shown to be more important than obesity as expressed by an elevated body mass index as a causative factor for the development of these diseases. In addition to the mechanical effects of obesity, such as an increase in intra-abdominal pressure from large amounts of adipose tissue, substances that adipose tissues secrete, such as tumor necrosis factor-α, interleukin-6, leptin, and insulin-like growth factor-1, have been proposed to be pathogenic links to these diseases. In this review, we discuss the association of metabolic syndrome or the individual components of metabolic syndrome, focusing on obesity and abdominal obesity, with gastrointestinal diseases.

Key words: visceral obesity, adipokines, GERD, esophageal adenocarcinoma, colorectal cancer

Introduction

Metabolic syndrome is a cluster of metabolic abnormalities and is defined as the presence of three or more of the following factors: abdominal obesity (increased waist circumference [WC]), elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, high blood pressure, and high fasting glucose. Metabolic syndrome is a risk factor for cardiovascular and other chronic diseases. Metabolic syndrome has been drawing increasing attention, and abdominal obesity, especially visceral obesity (i.e., the accumulation of intra-abdominal fat), has been suggested to be the most clinically important obesity pattern. Sensitive measures for visceral obesity are WC and the waist-to-hip ratio (WHR). Although many studies of the relationship between obesity and several gastrointestinal diseases have been performed, literature on whether metabolic syndrome or abdominal obesity is a risk factor for gastrointestinal diseases is scant. We review the association of metabolic syndrome, or the individual components of metabolic syndrome, focusing on obesity and abdominal obesity, with gastrointestinal diseases.

Gastroesophageal reflux disease, Barrett’s esophagus, and esophageal adenocarcinoma

Gastroesophageal reflux disease (GERD) and obesity are two of the most common diseases in the United States and the Western world, and the incidence of both have been increasing rapidly. Recently, GERD was shown to affect around 20% of the U.S. population. The prevalence of obesity [body mass index (BMI) ≥ 30 kg/m²] is 30.5% in the U.S. population. An association of symptoms of GERD with obesity has been reported, and increases in symptoms of GERD are correlated with increases in BMI. A cross-sectional population-based study from the United States by Lock et al. that assessed risk factors for development of GERD symptoms identified a BMI > 30 kg/m² as one risk factor [odds ratio (OR) 2.8; 95% confidence interval (CI), 1.7–4.5, compared with normal weight as defined by BMI ≤ 24 kg/m²]. A cross-sectional population-based study from the United Kingdom showed that BMI was strongly and positively related to the frequency of symptoms of GERD. The ORs for frequency of heartburn and acid regurgitation occurring

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at least once a week in obese people compared with those of normal weight were 2.91 (95% CI, 2.07–4.08) and 2.23 (95% CI, 1.44–3.45), respectively. A population-based study from Germany also concluded that being overweight or obese was significantly associated with GERD symptoms. On the other hand, a population-based study from Sweden found that the OR of people who had ever been obese or overweight (BMI ≥ 25 kg/m²) during adulthood, compared with those who were never obese or overweight, having recurrent symptoms of GERD was 0.99 (95% CI, 0.66–1.47), and no association was found between reflux symptoms and BMI.

In cross-sectional population-based studies, esophagogastroduodenoscopic examinations are not usually performed. Accordingly, participants with GERD, both nonerosive and erosive, Barrett’s esophagus (BE), esophageal adenocarcinoma (EAC), or other diseases are all included. This diversity of diagnoses may influence the results. In studies in which endoscopic examination was performed in patients with GERD symptoms, the mean BMI is significantly higher among those with erosive GERD than among those with nonerosive GERD. Van Oijen et al. studied the association between BMI and symptoms of GERD in a population referred for upper gastrointestinal endoscopy and found that obesity and symptoms of GERD and also obesity and erosive GERD tended to be associated. El-Serag et al. studied whether an association between obesity and symptoms of GERD persists after adjusting for other known GERD risk factors such as age, sex, race, and smoking. A BMI > 30 kg/m² was associated with weekly heartburn or regurgitation (adjusted OR, 2.44; 95% CI, 1.27–4.67, compared with BMI < 25 kg/m²). Both being overweight (BMI, 25–30 kg/m²) and obesity were strong independent risk factors for erosive GERD. However, Lundell et al. reported that being massively overweight (BMI, 42.5 ± 5.2 kg/m²) was not associated with abnormal acid reflux or erosive GERD. Nilsson et al. reported a sex difference in the association between obesity and GERD symptoms. Although they found a positive dose–response association between higher BMI and GERD symptoms in both sexes, the association was stronger in female patients. Moreover, the degree of association differed between premenopausal and postmenopausal women, with the association stronger in premenopausal women. In a recent meta-analysis of published data on the association between obesity and GERD, both being overweight (BMI, 25–30 kg/m²) and obesity (BMI > 30 kg/m²) were associated with 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, and being overweight or obese was a risk factor for erosive GERD (OR, 1.76; 95% CI, 1.156–2.677).

In accordance with empirical observations, weight loss is often recommended to reduce GERD symptoms. If there is a direct association between obesity and GERD, GERD symptoms or the degree of erosive GERD should be altered by weight change, and the findings of Nilsson et al. support this hypothesis. They showed that the risk of reflux symptoms was increased (OR, 2.7; 95% CI, 2.3–3.2) among persons who gained more than 3.5 BMI units, compared with persons with stable BMI, while the risk of GERD symptoms was decreased (OR, 0.6; 95% CI, 0.4–0.9) among persons who lost more than 3.5 BMI units. However, data on the association of improvement of GERD symptoms with weight reduction are conflicting, with some reports showing improvement of GERD symptoms and others showing no improvement. The reason for the inconsistent results might be that the weight reduction was insufficient to effect an improvement or that irreversible changes at the esophagogastroduodenal junction, such as a hiatal hernia, may have followed an increase in BMI.

Assessment of the association of BMI and GERD involves many confounding factors. The association of obesity with GERD remains controversial, although much data indicate an increased risk of GERD in overweight or obese subjects. Recently, WC was reported to be associated with esophageal acid exposure to the same degree as BMI. After adjusting for WC, a BMI ≥ 30 kg/m² was no longer significantly associated with any measures of esophageal acid exposure. Consequently, abdominal obesity may be a more important causative factor for development of GERD symptoms than obesity as expressed by an elevated BMI. More studies are needed to test this hypothesis.

The incidence of adenocarcinoma of the esophagus has been steadily increasing over the past three decades in the United States and other parts of the Western world, whereas that of squamous cell carcinoma of the esophagus has remained stable. Among white men, the incidence of EAC rose most prominently. Although a rising incidence has also been observed in white women and black men, sex and race differences in the incidence still exist: the male:female incidence ratio is 8:1, and the white:black ratio is approximately 5:1. The reasons for these differences are insufficiently understood. GERD is known to be a risk factor for EAC, and obesity is also thought to be a risk factor, because of the increasing incidence of EAC in parallel with the rapid increase in obese persons, coupled with the fact that obesity is known to be a risk factor for many cancers in Western countries. This supposition is supported by several case–control studies. A meta-analysis conducted by Hampel et al. showed that both being overweight (BMI, 25–30 kg/m²) and obesity (BMI > 30 kg/m²) were associated with a statistically significant increase in the risk for EAC (OR, 1.52; 95% CI, 1.52–3.72).